Appendix A. Search Strategies

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1988 to November Week 3 2013>
Search Strategy:
---
1 exp Fatigue Syndrome, Chronic/
2 exp Encephalomyelitis/
3 exp Fatigue/
4 2 and 3
5 1 or 4
6 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7 (myalg$ adj3 encephal$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8 6 or 7
9 5 or 8
10 limit 9 to english language
11 limit 9 to abstracts
12 10 or 11

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2013>
Search Strategy:
---
1 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 (myalg$ adj3 encephal$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 1 or 2

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 2013>
Search Strategy:
---
1 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, abstract, full text, keywords, caption text]
2 (myalg$ adj3 encephal$).mp. [mp=title, abstract, full text, keywords, caption text]
3 1 or 2

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2013>
Search Strategy:
---
1 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, full text, keywords]
2 (myalg$ adj3 encephal$).mp. [mp=title, full text, keywords]
3 1 or 2

Appendix A. Search Strategies

Database: EBM Reviews - Health Technology Assessment <4th Quarter 2013>
Search Strategy:
---
1 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, text, subject heading word]
2 (myalg$ adj3 encephal$).mp. [mp=title, text, subject heading word]
3 1 or 2

Database: EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2013>
Search Strategy:
---
1 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, text, subject heading word]
2 (myalg$ adj3 encephal$).mp. [mp=title, text, subject heading word]
3 1 or 2

Database: PsycINFO <1988 to January Week 2 2014>
Search Strategy:
---
1 exp Chronic Fatigue Syndrome/
2 exp Encephalomyelitis/
3 exp Fatigue/
4 2 and 3
5 1 or 4
6 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
7 (myalg$ adj3 encephal$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
8 6 or 7
9 5 or 8
10 limit 9 to english language
11 limit 9 to abstracts
12 10 or 11

Appendix B. Inclusion and Exclusion Criteria

	Include	Exclude
Population	KQ 1: Symptomatic adults ≥18 years old with fatigue KQ 2: Symptomatic adults ≥18 years, diagnosed with ME, CFS, or both and without another underlying diagnosis	All KQs: Populations containing children or adolescents. Patients with another underlying diagnosis.
Interventions	KQ 1: Case definitions (e.g., Fukuda/CDC, Canadian, International, and others) KQ 2: Forms of counseling and behavior therapy, graded exercise programs, complementary and alternative medicine (acupuncture, relaxation, massage, other), and symptom-based medication management (immune modulators, beta blockers, antidepressants, anxiolytics, stimulants, other)	KQ 2: Medications not available in the U.S.
Comparators	KQ 1: Diagnostic accuracy studies and diagnostic concordance studies KQ 2: Placebo, no treatment, usual care, other active interventions (including combination therapies and head-to-head trials)	KQ 1: No comparator KQ 2: No comparator
Outcomes	KQ 1: Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, C statistic (AUROC), net reclassification index; concordance, any potential harm from diagnosis (such as psychological harms, labeling, risk from diagnostic test, misdiagnosis, other) KQ 2: Overall function (i.e. 36-item Short Form Survey), quality of life, days spent at work/school, proportion working full- or part-time, fatigue (Multidimensional Fatigue Inventory or similar), adverse effects of interventions, withdrawals and withdrawals due to adverse events, rates of adverse events due to interventions	KQ 1: Not listed as an included outcome KQ 2: Not listed as an included outcome
Settings	All KQs: Clinical settings and those generalizable to a U.S. primary care setting	All KQs: Studies performed in countries with populations not similar to the U.S.; studies conducted in schools or work-sites, unless primary-care feasible
Timing	KQ 1: Any duration KQ 2: ≥12 weeks of treatment	KQ 1: None KQ 2: <12 weeks of treatment
Study types and designs	All KQ: Studies published in 1988 or after KQ 2: Systematic reviews or meta-analyses of randomized or controlled clinical trials, primary reports of randomized or controlled clinical trials, and large cohort studies	All KQ: Non-systematic reviews, letters to the editor, before and after studies, case-control studies, non-comparative studies; reviews not in English; and studies published before 1988

AUROC = area under the receiver operating characteristics curve; CDC = Centers for Disease Control and Prevention; CFS = chronic fatigue syndrome; KQ = key question; ME = myalgic encephalomyelitis; U.S. = United States

Appendix C. List of Included Studies

Asbring P, Narvanen A-L. Women's experiences of stigma in relation to chronic fatigue syndrome and fibromyalgia. Qual Health Res. 2002;12(2): 148-60. PMID: 11837367.

Aslakson E, Vollmer-Conna U, White PD. The validity of an empirical delineation of heterogeneity in chronic unexplained fatigue. Pharmacogenomics. 2006;7(3): 365-73. PMID: 16610947.

Assefi NP, Coy TV, Uslan D, et al. Financial, occupational, and personal consequences of disability in patients with chronic fatigue syndrome and fibromyalgia compared to other fatiguing conditions. J Rheumatol. 2003;30(4): 804-8. PMID: 12672203.

Bazelmans E, Prins JB, Lulofs R, et al. Cognitive behaviour group therapy for chronic fatigue syndrome: a non-randomised waiting list controlled study. Psychother Psychosom. 2005;74(4): 218-24. PMID: 15947511.

Blacker CVR, Greenwood DT, Wesnes KA, et al. Effect of galantamine hydrobromide in chronic fatigue syndrome: a randomized controlled trial. JAMA. 2004;292(10): 1195-204. PMID: 15353532.

Blockmans D, Persoons P, Van Houdenhove B, et al. Combination therapy with hydrocortisone and fludrocortisone does not improve symptoms in chronic fatigue syndrome: a randomized, placebo-controlled, double-blind, crossover study. Am J Med. 2003;114(9): 736-41. PMID: 12829200.

Brown AA, Evans MA, Jason LA. Examining the energy envelope and associated symptom patterns in chronic fatigue syndrome: Does coping matter? Chronic Illn. 2013;9(4): 302-11. PMID: 23585632.

Brown AA, Jason LA, Evans MA, et al. Contrasting case definitions: The ME International Consensus Criteria vs. the Fukuda et al. CFS criteria. N Am J Psychol. 2013;15(1): 103-20.

Burgess M, Andiappan M, Chalder T. Cognitive behaviour therapy for chronic fatigue syndrome in adults: face to face versus telephone treatment: a randomized controlled trial. Behav Cogn Psychother. 2012;40(2): 175-91. PMID: 21929831.

Davenport TE, Stevens SR, Baroni K, et al. Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue. Disabil Rehabil. 2011;33(25-26): 2596-604. PMID: 21682669.

Davenport TE, Stevens SR, Baroni K, et al. Diagnostic accuracy of symptoms characterising chronic fatigue syndrome. Disabil Rehabil. 2011;33(19-20): 1768-75. PMID: 21208154.

Deale A, Chalder T, Marks I, et al. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. Am J Psychiatry. 1997;154(3): 408-14. PMID: 9054791.

Deale A, Husain K, Chalder T, et al. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. Am J Psychiatry. 2001;158(12): 2038-42. PMID: 11729022.

Deale A, Wessely S. Diagnosis of psychiatric disorder in clinical evaluation of chronic fatigue syndrome. J R Soc Med. 2000;93(6): 310-2. PMID: 10911826.

Diaz-Mitoma F, Turgonyi E, Kumar A, et al. Clinical improvement in chronic fatigue syndrome is associated with enhanced natural killer cell-mediated cytotoxicity: The results of a pilot study with Isoprinosine. J Chronic Fatigue Syndr. 2003;11(2): 71-93.

Dickson A, Knussen C, Flowers P. Stigma and the delegitimation experience: An interpretative phenomenological analysis of people living with chronic fatigue syndrome. Psychol Health. 2007;22(7): 851-67.

Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. BMJ. 1997;314(7095): 1647-52. PMID: 9180065.

Gaab J, Engert V, Heitz V, et al. Associations between neuroendocrine responses to the Insulin Tolerance Test and patient characteristics in chronic fatigue syndrome. J Psychosom Res. 2004;56(4): 419-24. PMID: 15094026.

Gaab J, Huster D, Peisen R, et al. Low-dose dexamethasone suppression test in chronic fatigue syndrome and health. Psychosom Med. 2002;64(2): 311-8. PMID: 11914448.

Gaab J, Rohleder N, Heitz V, et al. Stress-induced changes in LPS-induced pro-inflammatory cytokine production in chronic fatigue syndrome. Psychoneuroendocrinology. 2005;30(2): 188-98. PMID: 15471616.

Goudsmit EM, Ho-Yen DO, Dancey CP. Learning to cope with chronic illness. Efficacy of a multi-component treatment for people with chronic fatigue syndrome. Patient Educ Couns. 2009;77(2): 231-6. PMID: 19576714.

Green J, Romei J, Natelson BH. Stigma and chronic fatigue syndrome. J Chronic Fatigue Syndr. 1999;5(2): 63-95.

Guise J, McVittie C, McKinlay A. A discourse analytic study of ME/CFS (Chronic Fatigue Syndrome) sufferers' experiences of interactions with doctors. J Health Psychol. 2010;15(3): 426-35. PMID: 20348363.

Hadzi-Pavlovic D, Hickie IB, Wilson AJ, et al. Screening for prolonged fatigue syndromes: validation of the SOFA scale. Soc Psychiatry Psychiatr Epidemiol. 2000;35(10): 471-9. PMID: 11127722.

Hlavaty LE, Brown MM, Jason LA. The effect of homework compliance on treatment outcomes for participants with myalgic encephalomyelitis/chronic fatigue syndrome. Rehabil Psychol. 2011;56(3): 212-8. PMID: 21767035.

Ho RTH, Chan JSM, Wang C-W, et al. A randomized controlled trial of qigong exercise on fatigue symptoms, functioning, and telomerase activity in persons with chronic fatigue or chronic fatigue syndrome. Ann Behav Med. 2012;44(2): 160-70. PMID: 22736201.

Hobday RA, Thomas S, O'Donovan A, et al. Dietary intervention in chronic fatigue syndrome. J Hum Nutr Diet. 2008;21(2): 141-9. PMID: 18339054.

Jason L, Benton M, Torres-Harding S, et al. The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS. Patient Educ Couns. 2009;77(2): 237-41. PMID: 19356884.

Jason L, Brown M, Evans M, et al. Measuring substantial reductions in functioning in patients with chronic fatigue syndrome. Disabil Rehabil. 2011;33(7): 589-98. PMID: 20617920.

Jason LA, Brown A, Clyne E, et al. Contrasting case definitions for chronic fatigue syndrome, Myalgic Encephalomyelitis/chronic fatigue syndrome and myalgic encephalomyelitis. Eval Health Prof. 2012;35(3): 280-304. PMID: 22158691.

Jason LA, Brown A, Evans M, et al. Contrasting chronic Fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome. Fatigue. 2013;1(3)PMID: 23914329.

Jason LA, Evans M, Brown A, et al. Sensitivity and specificity of the CDC empirical chronic fatigue syndrome case definition. Psychology. 2010;1(1): 9-16. PMID: 23685416.

Jason LA, Roesner N, Porter N, et al. Provision of social support to individuals with chronic fatigue syndrome. J Clin Psychol. 2010;66(3): 249-58. PMID: 19902489.

Jason LA, Taylor RR. Measuring attributions about chronic fatigue syndrome. J Chronic Fatigue Syndr. 2001;8(3-4): 31-40.

Jason LA, Taylor RR, Stepanek Z, et al. Attitudes regarding chronic fatigue syndrome: The importance of a name. J Health Psychol. 2001;6(1): 61-71. PMID: 22049238.

Jason LA, Torres-Harding S, Friedberg F, et al. Non-pharmacologic interventions for CFS: a randomized trial. J Clin Psychol Med Settings. 2007;14(4): 275-96.

Jason LA, Torres-Harding SR, Taylor RR, et al. A comparison of the 1988 and 1994 diagnostic criteria for chronic fatigue syndrome. J Clin Psychol Med Settings. 2001;8(4): 337-43.

Katon WJ, Buchwald DS, Simon GE, et al. Psychiatric illness in patients with chronic fatigue and those with rheumatoid arthritis. J Gen Intern Med. 1991;6(4): 277-85. PMID: 1890495.

Knoop H, van der Meer JWM, Bleijenberg G. Guided self-instructions for people with chronic fatigue syndrome: randomised controlled trial. Br J Psychiatry. 2008;193(4): 340-1. PMID: 18827302.

Komaroff AL, Fagioli LR, Doolittle TH, et al. Health status in patients with chronic fatigue syndrome and in general population and disease comparison groups. Am J Med. 1996;101(3): 281-90. PMID: 8873490.

Lewis I, Pairman J, Spickett G, et al. Is chronic fatigue syndrome in older patients a different disease? -- a clinical cohort study. Eur J Clin Invest. 2013;43(3): 302-8. PMID: 23397955.

Linder R, Dinser R, Wagner M, et al. Generation of classification criteria for chronic fatigue syndrome using an artificial neural network and traditional criteria set. In Vivo. 2002;16(1): 37-43. PMID: 11980359.

Lopez C, Antoni M, Penedo F, et al. A pilot study of cognitive behavioral stress management effects on stress, quality of life, and symptoms in persons with chronic fatigue syndrome. J Psychosom Res. 2011;70(4): 328-34. PMID: 21414452.

McKenzie R, O'Fallon A, Dale J, et al. Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. JAMA. 1998;280(12): 1061-6. PMID: 9757853.

Montoya JG, Kogelnik AM, Bhangoo M, et al. Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome. J Med Virol. 2013;85(12): 2101-9. PMID: 23959519.

Moss-Morris R, Sharon C, Tobin R, et al. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. J Health Psychol. 2005;10(2): 245-59. PMID: 15723894.

Núñez M, Fernandez-Sola J, Nunez E, et al. Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural therapy and graded exercise versus usual treatment. A randomised controlled trial with 1year of follow-up. Clin Rheumatol. 2011;30(3): 381-9. PMID: 21234629.

Ockerman PA. Antioxidant treatment of chronic fatigue syndrome. Clin Pract Alternat Med. 2000;1(2): 88-91.

O'Dowd H, Gladwell P, Rogers CA, et al. Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. Health Technol Assess. 2006;10(37): iii-iv, ix-x, 1-121. PMID: 17014748.

Peterson PK, Shepard J, Macres M, et al. A controlled trial of intravenous immunoglobulin G in chronic fatigue syndrome. Am J Med. 1990;89(5): 554-60. PMID: 2239975.

Prins JB, Bleijenberg G, Bazelmans E, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet. 2001;357(9259): 841-7. PMID: 11265953.

Sharpe M, Hawton K, Simkin S, et al. Cognitive behaviour therapy for the chronic fatigue syndrome: a randomized controlled trial. BMJ. 1996;312(7022): 22-6. PMID: 8555852.

Strayer DR, Carter WA, Brodsky I, et al. A controlled clinical trial with a specifically configured RNA drug, poly(I) midline dot poly(C12U), in chronic fatigue syndrome. Clin Infect Dis. 1994;18(SUPPL. 1): S88-S95. PMID: 8148460.

Strayer DR, Carter WA, Stouch BC, et al. A double-blind, placebo-controlled, randomized, clinical trial of the TLR-3 agonist rintatolimod in severe cases of chronic fatigue syndrome. PLoS ONE. 2012;7(3): e31334. PMID: 22431963.

Sutcliffe K, Gray J, Tan MP, et al. Home orthostatic training in chronic fatigue syndrome--a randomized, placebo-controlled feasibility study. Eur J Clin Invest. 2010;40(1): 18-24. PMID: 19912315.

Taylor RR. Quality of life and symptom severity for individuals with chronic fatigue syndrome: findings from a randomized clinical trial. Am J Occup Ther. 2004;58(1): 35-43. PMID: 14763634.

The GKH, Bleijenberg G, van der Meer JWM. The effect of acclydine in chronic fatigue syndrome: A randomized controlled trial. PLoS Clinical Trials. 2007;2(5): e19TN: ISRCTN77271661/ISRCTN. PMID: 17525791.

Tiev KP, Demettre E, Ercolano P, et al. RNase L levels in peripheral blood mononuclear cells: 37-kilodalton/83-kilodalton isoform ratio is a potential test for chronic fatigue syndrome. Clin Diagn Lab Immunol. 2003;10(2): 315-6. PMID: 12626460.

Tummers M, Knoop H, Bleijenberg G. Effectiveness of stepped care for chronic fatigue syndrome: a randomized noninferiority trial. J Consult Clin Psychol. 2010;78(5): 724-31. PMID: 20873907.

Tummers M, Knoop H, van Dam A, et al. Implementing a minimal intervention for chronic fatigue syndrome in a mental health centre: a randomized controlled trial. Psychol Med. 2012;42(10): 2205-15. PMID: 22354999.

Tummers M, Knoop H, van Dam A, et al. Moderators of the treatment response to guided self-instruction for chronic fatigue syndrome. J Psychosom Res. 2013;74(5): 373-7. PMID: 23597323.

Van Hoof E, De Meirleir K. Chronic Fatigue Syndrome and Myalgic Encephalomyletis: Are Both Conditions on the Same Continuum? N Am J Psychol. 2005;7(2): 189-204.

Vermeulen RCW, Scholte HR. Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. Psychosom Med. 2004;66(2): 276-82. PMID: 15039515.

Walach H, Bosch H, Lewith G, et al. Effectiveness of distant healing for patients with chronic fatigue syndrome: a randomised controlled partially blinded trial (EUHEALS). Psychother Psychosom. 2008;77(3): 158-66. PMID: 18277062.

Wearden AJ, Dowrick C, Chew-Graham C, et al. Nurse led, home based self help treatment for patients in primary care with chronic fatigue syndrome: randomised controlled trial. BMJ. 2010;340: c1777. PMID: 20418251.

Wearden AJ, Dunn G, Dowrick C, et al. Depressive symptoms and pragmatic rehabilitation for chronic fatigue syndrome. Br J Psychiatry. 2012;201(3): 227-32. PMID: 22844025.

Wearden AJ, Emsley R. Mediators of the effects on fatigue of pragmatic rehabilitation for chronic fatigue syndrome. J Consult Clin Psychol. 2013;81(5): 831-8. PMID: 23796316.

Wearden AJ, Morriss RK, Mullis R, et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome.[Erratum appears in Br J Psychiatry 1998 Jul;173:89]. Br J Psychiatry. 1998;172: 485-90. PMID: 9828987.

Weatherley-Jones E, Nicholl JP, Thomas KJ, et al. A randomised, controlled, triple- blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome. J Psychosom Res. 2004;56(2): 189-97. PMID: 15016577.

White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet. 2011;377(9768): 823-36. PMID: 21334061.

Williams G, Waterhouse J, Mugarza J, et al. Therapy of circadian rhythm disorders in chronic fatigue syndrome: no symptomatic improvement with melatonin or phototherapy. Eur J Clin Invest. 2002;32(11): 831-7. PMID: 12423324.

Appendix D. List of Excluded Studies

Key to exclusion codes

2,3,4	Excluded because the study does not address a Key Question or meet inclusion criteria, but full text pulled to provide background information
5	Wrong population
6	Wrong intervention
7	Wrong outcomes
8	Wrong study design for Key Question
9	Wrong publication type
10	Foreign language
11	Not a human population
12	Inadequate duration
13	Study published before 1988
14	Review not meeting our requirements

A Report of the CFS/ME Working Group. Available at: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4064945.pdf. Accessed July 3, 2014.
Exclusion code: 9

Alleged link between hepatitis B vaccine and chronic fatigue syndrome. CMAJ. 1992;146(1):37-8. PMID: 1530818.
Exclusion code: 2

Cognitive behavioral therapy and exercise for chronic fatigue syndrome. J Pain Pall Care Pharmacother. 2002;16(3):110-1. PMID: 14640363.
Exclusion code: 9

From the Centers for Disease Control and Prevention. Inability of retroviral tests to identify persons with chronic fatigue syndrome, 1992. JAMA. 1993;269(14):1779. PMID: 8459495.
Exclusion code: 5

Government Response to the CFS/ME Independent Working Group's Report. Available at: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4059507.pdf. Accessed July 3, 2014.
Exclusion code: 9

Managing my M.E. What people with ME/CFS and their carers want from the UK's health and social Services. The ME Association. Gawcott, England. Available at: http://www.meassociation.org.uk/wp-content/uploads/MEA-Management-Survey-2010.pdf. Accessed June 23, 2014.
Exclusion code: 9

Report of the working group on the possible relationship between hepatitis B vaccination and the chronic fatigue syndrome. CMAJ. 1993;149(3):314-9. PMID: 8339178.
Exclusion code: 2

Appendix D. List of Excluded Studies

Aaron LA, Arguelles LM, Ashton S, et al. Health and functional status of twins with chronic regional and widespread pain.[Erratum appears in J Rheumatol. 2002 Dec;29(12):2667 Note: Buchwald, Dedra [corrected to Buchwald, Debra]]. J Rheumatol. 2002;29(11):2426-34. PMID: 12415604.
Exclusion code: 8

Aaron LA, Buchwald D. Fibromyalgia and other unexplained clinical conditions. Curr Rheumatol Rep. 2001;3(2):116-22. PMID: 11286667.
Exclusion code: 2

Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med. 2001;134(9 Pt 2):868-81. PMID: 11346323.
Exclusion code: 3

Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Intern Med. 2000;160(2):221-7. PMID: 10647761.
Exclusion code: 3

Aaron LA, Herrell R, Ashton S, et al. Comorbid clinical conditions in chronic fatigue: a co-twin control study. J Gen Intern Med. 2001;16(1):24-31. PMID: 11251747.
Exclusion code: 3

Abbey SE. Psychotherapeutic perspectives on chronic fatigue syndrome. Chronic fatigue syndrome: An integrative approach to evaluation and treatment. New York, NY: Guilford Press; 1996:185-211.

Abbey SE, Garfinkel PE. Chronic fatigue syndrome and depression: cause, effect, or covariate. Rev Infect Dis. 1991;13 Suppl 1:S73-83. PMID: 2020805.
Exclusion code: 2

Abbey SE, Toner BB, Garfinkel PE, et al. Self-report symptoms that predict major depression in patients with prominent physical symptoms. Int J Psychiatry Med. 1990;20(3):247-58. PMID: 2265887.
Exclusion code: 5

Abdel-Khalek AM. Chronic fatigue syndrome and its association with obsession compulsion among a non-clinical sample using questionnaires. J Chronic Fatigue Syndr. 2008;14(3):89-100.
Exclusion code: 2

Adams D, Wu T, Yang X, et al. Traditional Chinese medicinal herbs for the treatment of idiopathic chronic fatigue and chronic fatigue syndrome. Cochrane Database Syst Rev. 2009(4):CD006348. PMID: 19821361.
Exclusion code: 14

Adolphe AB. Chronic fatigue syndrome: possible effective treatment with nifedipine. Am J Med. 1988;85(6):892. PMID: 2848418.
Exclusion code: 8

Afari N, Buchwald D. Chronic fatigue syndrome: a review. Am J Psychiatry. 2003;160(2):221-36. PMID: 12562565.
Exclusion code: 14

Akarsu S, Tekin L, Ay H, et al. The efficacy of hyperbaric oxygen therapy in the management of chronic fatigue syndrome. Undersea Hyperb Med. 2013;40(2):197-200. PMID: 23682549.
Exclusion code: 12

Alraek T, Lee MS, Choi T-Y, et al. Complementary and alternative medicine for patients with chronic fatigue syndrome: a systematic review. BMC Altern Med. 2011;11:87. PMID: 21982120.
Exclusion code: 14

Amel Kashipaz MR, Swinden D, Todd I, et al. Normal production of inflammatory cytokines in chronic fatigue and fibromyalgia syndromes determined by intracellular cytokine staining in short-term cultured blood mononuclear cells. Clin Exp Immunol. 2003;132(2):360-5. PMID: 12699429.
Exclusion code: 5

Amsterdam JD, Shults J, Rutherford N. Open-label study of s-citalopram therapy of chronic fatigue syndrome and co-morbid major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(1):100-6. PMID: 17804135.
Exclusion code: 8

Andersen MM, Permin H, Albrecht F. Illness and disability in Danish Chronic Fatigue Syndrome patients at diagnosis and 5-year follow-up. J Psychosom Res. 2004;56(2):217-29. PMID: 15016582.
Exclusion code: 2

Andersson M, Bagby J, Dyrehag L, et al. Effects of staphylococcus toxoid vaccine on pain and fatigue in patients with fibromyaigia/chronic fatigue syndrome. Eur J Pain. 1998;2(2):133-42. PMID: 10700309.
Exclusion code: 5

Andersson M, Bagby JR, Dyrehag L, et al. Effects of staphylococcus toxoid vaccine on pain and fatigue in patients with fibromyalgia/chronic fatigue syndrome. Eur J Pain. 1998;2(2):133-42. PMID: 10700309.
Exclusion code: 5

Anfinson TJ. Diagnostic assessment of chronic fatigue syndrome. Medical-psychiatric practice, Vol 3. 1995:215-55.
Exclusion code: 2

Appleby L. Aerobic exercise and Fluoxetine in the treatment of chronic fatigue syndrome. National Research Register. 1995
Exclusion code: 9

Arroll MA, Senior V. Individuals' experience of chronic fatigue syndrome/myalgic encephalomyelitis: An interpretative phenomenological analysis. Psychol Health. 2008;23(4):443-58.
Exclusion code: 8

Ash-Bernal R, Wall C, 3rd, Komaroff AL, et al. Vestibular function test anomalies in patients with chronic fatigue syndrome. Acta Otolaryngol (Stockh). 1995;115(1):9-17. PMID: 7762393.
Exclusion code: 2

Awdry R. Homoeopathy may help ME. International Journal of Alternative and Complementary Medicine. 1996
Exclusion code: 9

Bagnall AM, Whiting P, Richardson R, et al. Interventions for the treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis. Qual Saf Health Care. 2002;11(3):284-8. PMID: 12486997.
Exclusion code: 14

Bakker RJ, van de Putte EM, Kuis W, et al. Effects of an educational video film in fatigued children and adolescents: a randomised controlled trial. Arch Dis Child. 2011;96(5):457-60. PMID: 20861404.
Exclusion code: 5

Baraniuk JN, Petrie KN, Le U, et al. Neuropathology in rhinosinusitis. Am J Respir Crit Care Med. 2005;171(1):5-11. PMID: 15477496.
Exclusion code: 8

Barron DF, Cohen BA, Geraghty MT, et al. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. J Pediatr. 2002;141(3):421-5. PMID: 12219066.
Exclusion code: 5

Baschetti R. Treating chronic fatigue with exercise. Results are contradictory for patients meeting different diagnostic criteria. BMJ. 1998;317(7158):600. PMID: 9758491.
Exclusion code: 9

Baschetti R. Investigations of hydrocortisone and fludrocortisone in the treatment of chronic fatigue syndrome. J Clin Endocrinol Metab. 1999;84(6):2263-4. PMID: 10372750.
Exclusion code: 9

Baschetti R. The 1microg Synacthen test in chronic fatigue syndrome. Clin Endocrinol (Oxf). 2000;52(6):797-9. PMID: 10848890.
Exclusion code: 9

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Randomized Controlled Trials

Criteria:

- Initial assembly of comparable groups**:**
  - adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: intention-to-treat analysis.

Definition of ratings based on above criteria:

Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study (followup at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and intention-to-treat analysis is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and intention-to-treat analysis is done for RCTs.

Poor: Studies will be graded "poor" if any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and intention-to-treat is lacking.

Diagnostic/Concordance Studies

Criteria:

- Test applied to an appropriate spectrum of patients (with and without disease/condition), avoiding case-control design
- Population tested was consecutive or random
- Clear eligibility criteria described and rigorous assessment of disease/condition
- Attrition reported and minimal loss to followup
- Test is adequately described and reproducible
- Test was validated in a second population group
- Test is an available standard case definition
- Diagnostic test is applied to all patients
- Blinding of outcome assessors to the reference standard

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 500) broad-spectrum patients with and without disease; study attempts to enroll a random or consecutive sample of patients who meet inclusion criteria screening cutoffs pre-stated.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (100 to 500 subjects) and a "medium" spectrum of patients (i.e. applicable to many settings where the diagnostic test would be applied).

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; small sample size (<100) of very narrow selected spectrum of patients (components of study not well described).

Sources: USPSTF Procedure Manual[1], AHRQ Methods Guide,[2] and AHRQ Methods Guide for Medical Test Reviews[3]

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Strength of Evidence Criteria[1]

The set of five required domains comprises the main constructs that Evidence-based Practice Centers (EPCs) should use for all major outcomes and comparisons of interest. As briefly defined below in Table 1, these domains represent related but separate concepts, and each is scored independently. The concepts are explained in more detail in below.

Table 1. Required domains and their definitions

Domain	Definition and Elements	Score and Application
Study Limitations	Study limitations is the degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements: • Study design: Whether RCTs or other designs such as nonexperimental or observational studies. • Study conduct. Aggregation of ratings of risk of bias of the individual studies under consideration.	Score as one of three levels, separately by type of study design: • Low level of study limitations • Medium level of study limitations • High level of study limitations
Directness	Directness relates to (a) whether evidence links interventions directly to a health outcome of specific importance for the review, and (b) for comparative studies, whether the comparisons are based on head-to-head studies. The EPC should specify the comparison and outcome for which the SOE grade applies. Evidence may be indirect in several situations such as: • The outcome being graded is considered intermediate (such as laboratory tests) in a review that is focused on clinical health outcomes (such as morbidity, mortality). • Data do not come from head-to-head comparisons but rather from two or more bodies of evidence to compare interventions A and B—e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not direct comparisons of A vs. B. • Data are available only for proxy respondents (e.g., obtained from family members or nurses) instead of directly from patients for situations in which patients are capable of self-reporting and self-report is more reliable. Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcome.	Score as one of two levels: • Direct • Indirect If the domain score is indirect, EPCs should specify what type of indirectness accounts for the rating.
Consistency	Consistency is the degree to which included studies find either the same direction or similar magnitude of effect. EPCs can assess this through two main elements: • Direction of effect: Effect sizes have the same sign (that is, are on the same side of no effect or a minimally important difference [MID]) • Magnitude of effect: The range of effect sizes is similar. EPCs may consider the overlap of CIs when making this evaluation. The importance of direction vs. magnitude of effect will depend on the key question and EPC judgments.	Score as one of three levels: • Consistent • Inconsistent • Unknown (e.g., single study) Single-study evidence bases (including mega-trials) cannot be judged with respect to consistency. In that instance, use "Consistency unknown (single study)."

Domain	Definition and Elements	Score and Application
Precision	Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome, based on the sufficiency of sample size and number of events. • A body of evidence will generally be imprecise if the optimal information size (OIS) is not met. OIS refers to the minimum number of patients (and events when assessing dichotomous outcomes) needed for an evidence base to be considered adequately powered. • If EPCs performed a meta-analysis, then EPCs may also consider whether the CI crossed a threshold for an MID. • If a meta-analysis is infeasible or inappropriate, EPCs may consider the narrowness of the range of CIs or the significance level of p-values in the individual studies in the evidence base.	Score as one of two levels: • Precise • Imprecise A precise estimate is one that would allow users to reach a clinically useful conclusion (e.g., treatment A is more effective than treatment B).
Reporting Bias	Reporting bias results from selectively publishing or reporting research findings based on the favorability of direction or magnitude of effect. It includes: • Study publication bias, i.e., nonreporting of the full study. • Selective outcome reporting bias, i.e., nonreporting (or incomplete reporting) of planned outcomes or reporting of unplanned outcomes. • Selective analysis reporting bias, i.e., reporting of one or more favorable analyses for a given outcome while not reporting other, less favorable analyses. Assessment of reporting bias for individual studies depends on many factors–e.g. availability of study protocols, unpublished study documents, and patient-level data. Detecting such bias is likely with access to all relevant documentation and data pertaining to a journal publication, but such access is rarely available. Because methods to detect reporting bias in observational studies are less certain, this guidance does not require EPCs to assess it for such studies.	Score as one of two levels: • Suspected • Undetected Reporting bias is suspected when: • Testing for funnel plot asymmetry demonstrates a substantial likelihood of bias, And/or • A qualitative assessment suggests the likelihood of missing studies, analyses, or outcomes data that may alter the conclusions from the reported evidence. Undetected reporting bias includes all alternative scenarios.

CI = confidence internal; EPC = Evidence-based Practice Center; MID = minimally important difference; OIS = optimal information size; SOE = strength of evidence

Study Limitations Domain

Definition

Scoring the study limitations domain is the essential starting place for grading strength of the body of evidence. It refers to the judgment that the findings from included studies of a treatment (or treatment comparison) for a given outcome are adequately protected against bias (i.e., have good internal validity), based on the design and conduct of those studies. That is, EPCs assess the ability of the evidence to yield an accurate estimate of the true effect without bias (nonrandom error).

Directness Domain

Definition

Directness of evidence expresses how closely available evidence measures an outcome of interest. Assessing directness has two parts: directness of outcomes and directness of

comparisons. Applicability of evidence (external validity) is considered explicitly but separately from strength of evidence.

Consistency Domain

Definition

Consistency refers to the degree of similarity in the direction of effects or the degree of similarity in the effect sizes (magnitudes of effect) across individual studies within an evidence base. EPCs may choose which of these two notions of consistency (direction or magnitude) they are scoring; they should be explicit about this choice.

Precision Domain

Definition

Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. It is based on the potential for random error evaluated through the sufficiency of sample size and, in the case of dichotomous outcomes, the number of events. A precise body of evidence should enable decisionmakers to draw conclusions about whether one treatment is inferior, equivalent, or superior to another.

Reporting Bias

Definition

Reporting bias occurs when authors, journals, or both decide to publish or report research findings based on their direction or magnitude of effect.52,53 Table 2 defines the three main types of reporting bias that either authors or journals can introduce: publication bias and outcome and analysis reporting bias.

Four Strength of Evidence Levels

The four levels of grades are intended to communicate to decisionmakers EPCs' confidence in a body of evidence for a single outcome of a single treatment comparison. Although assigning a grade requires judgment, having a common understanding of the interpretation will be useful for helping EPCs as they conduct their own global assessment and for improving consistency across reviewers and EPCs.

Table 2 summarizes the four levels of grades that EPCs use for the overall assessment of the body of evidence. Grades are denoted high, moderate, low, and insufficient. They are not designated by Roman numerals or other symbols. EPCs should apply discrete grades and should not use designations such as "low to moderate" strength of evidence.

Table 2. Strength of evidence grades and definitions

Grade	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome**. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Each level has two components. The first, principal definition concerns the level of confidence that EPCs place in the estimate of effect (direction or magnitude of effect) for the benefit or harm; this equates to their judgment as to how much the evidence reflects a true effect. The second, subsidiary definition involves an assessment of the level of deficiencies in the body of evidence and belief in the stability of the findings, based on domain scores and a more holistic, summary appreciation of the possibly complex interaction among the individual domains.

Assigning a grade of high, moderate, or low implies that an evidence base is available from which to estimate an effect for either the benefit or the harm. The designations of high, moderate, and low should convey how confident EPCs would be about decisions based on evidence of differing grades, which can be based on either quantitative or qualitative assessment.

For comparative effectiveness questions, the comparison is typically a choice of either direction (A>B, A=B, A<B) or magnitude (difference between A and B). In some instances assigning different grades regarding the direction and the magnitude of an effect may be appropriate. An example of this situation is when studies consistently find that an intervention improves an outcome (e.g., apnea-hypopnea index is reduced by a statistically significant amount or beyond a minimally important difference), but the degree of heterogeneity about the estimate is high (e.g., range -10 to -46 events/minute; $I^2 = 86\%$).

The importance of the distinctions among high, moderate, and low levels (and the distinction with insufficient strength of evidence) can vary by the type of outcome, comparison, and decisionmaker. EPCs understand that some stakeholders may want to take action only when evidence is of high or moderate strength, whereas others may want to understand clearly the implications of low versus insufficient evidence. Even when strength of evidence is low or insufficient, consumers, clinicians, and policymakers may find themselves in the position of having to make choices and decisions, and they may consider factors other than the evidence from a specific systematic review, such as patient values and preferences, costs, or resources.

References

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Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Objectives	Case definition	Study design/outcome measures
Brown, *et al.,* 2013[47]	To examine sub-types of individuals with CFS based on variables associated with energy envelope theory; to examine the role of coping strategies among the sub-types.	Revised CFS questionnaire based on CDC (Fukuda, 1994)	Cross-sectional analysis of 91 subjects at baseline. SF-36 (0-100 scale, higher scores indicate better health) Single item from the Chronic Fatigue Syndrome Medical Questionnaire: "rate the severity of your PEM over the past 6 months" to measure PEM severity (scored 0-100)* Energy envelope quotient. "rate weekly perceived energy and expended energy on a 100-point scale (0=no energy; 100=abundant energy.)† Coping measured by bCOPE
Davenport, *et al.,* 2011[45] "Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue"	To determine the validity and reliability of the SF-36 in sub-groups of individuals with fatigue.	CDC (Fukuda, 1994)	Each subject completed the SF-36 and MFI-20 prior to and 1 week after completing 2 maximal cardiopulmonary exercise tests approximately 24 hours apart. **Procedures:** pedaling for <1 minute, then workload was increased 15 watts/minute until voluntary exhaustion. **Outcomes:** Each subject completed a questionnaire with open-ended questions about recovery (operationally defined as full return to pre-test symptoms and activity levels).

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Total N/populations	Eligibility criteria/recruitment methods	Statistical methods
Brown, *et al.,* 2013[47]	114 recruited for RCT (Jason, et al., 2007); 91 contributed data to this study. United States; 83% female.	**Inclusion:** Patients with CFS who were >18 years old, not pregnant, English speaking, and physically able to attend sessions. **Exclusion:** Patients with data missing for key variables. **Recruitment:** Participants recruited from a variety of sources in the Chicago area: 46% physician recruitment, 34% media recruited, 20% other sources.	Cluster analysis: 2 step cluster analysis to explore potential clusters on physical functioning, PEM severity, and energy envelope quotient. All variables were standardized before clustering. Ward's Hierarchical clustering method was employed, then a K-Means non-hierarchical approach was used to examine multiple cluster solutions. Descriptive discriminant analysis conducted to investigate whether the use of different coping strategies could discriminate the three clusters.
Davenport, *et al.,* 2011[45] "Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue"	30;16 with CFS and 14 non-disabled sedentary controls. United States; 100% female.	**Inclusion:** Patients meeting CDC (Fukuda, 1994) criteria for CFS, as confirmed by a recruiting physician. **Exclusion:** Other fatiguing health conditions. **Recruitment:** 2 physicians who specialized in the clinical management of CFS referred subjects with CFS into the study. Another sample of otherwise non-disabled sedentary individuals (exercising to the point of perspiration 1 time per week or less) were recruited to participate as control subjects. Effort made to match CFS and control subjects on sex, age and BMI.	Pairwise comparison between groups, intraclass correlation coefficients for the SF-36 scores using formula 2.1. Strength of reproducibility among the variables based on Munro's criteria (very low=0.15-0.24, low=0.25-0.49, moderate=0.50-0.69, high=0.79-0.89, and very high=0.90-1.00). Content and concurrent validity assessed using Mann-Whitney U test for significance between means, and Spearman's rho for bivariate correlations. Predictive validity using ROC curve analysis to estimate the value of the SF-36 score needed to predict failure to achieve self-reported recovery following cardiopulmonary exercise tests at 1 day and 1 week. Sensitivity to change of SF-36 sub-scale scores determined by calculating minimal detectable change outside a 95% CI for each sub-scale.

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Findings	Conclusions
Brown, *et al.,* 2013[47]	3 cluster solution: Cluster 1: Symptomatic and Highly Overextended (n=20) Cluster 2: Less Symptomatic and Moderately Overextended (n=34) Cluster 3: Symptomatic and Mildly Overextended (n=37) Function 1 was significant and accounted for 10.3% of the variance between groups. All the coefficients for Function 1 were >0.30, indicating that each coping strategy was significantly associated with the function. Adaptive coping accounted for 56% of the variance explained by the function (also correlated at 0.88 suggesting that this measure is predominantly driving the function); and less adaptive coping accounted for 25% of the variance. Cluster 3 - the Symptomatic and Mildly Overextended group - are high in Function 1. (Function 1 adaptive: coefficient 0.88; R^2 56%; less adaptive coefficient 0.67, R^2 - 25%).	3 distinct groups were identified based on self reports of physical function, PEM severity, and energy envelope maintenance.
Davenport, *et al.,* 2011[45] "Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue"	The diagnostic accuracy of SF-36 v2 subscales to predict recovery within 1 week: ROC AUC analysis was significant for the role emotional (AUC: 0.875; 95% CI, 0.699 to 1.00, p<0.01), vitality (AUC: -0.792; 95% CI, 0.630 to 0.953, p<0.05) and bodily pain (AUC: 0.829; 95% CI, 0.681 to 0.977, p<0.01). Their cut scores were identified as 71%, 22%, and 39% respectively. **AUC (95% CI), sensitivity, specificity, positive likelihood ratio, negative likelihood ratio** *Subscales of SF-36 for failure to recover at 1 day* Physical function: 0.880 (0.697 to 1.00, p=0.001), 0.82, 0.82, 4.5, 0.21 Role physical : 0.865 (0.706 to 1.00, p=0.001), 0.79, 0.88, 6.9, 0.23 Bodily pain: 0.911 (0.764 to 1.00, p<0.001), 0.85, 0.81, 4.4, 0.18 General health: 0.898 (0.000 to 1.00, p<0.001), 0.85, 0.81, 4.4, 0.18 Role emotional 0.659 (0.449 to 0.869, p=0.157) Vitality: 0.836 (0.672 to 1.00, p=0.003), 0.85, 0.81, 4.4, 0.18 Social function: 0.854 (0.695 to 1.00, p=0.002), 0.79, 0.90, 7.9, 0.23 Mental health: 0.672 (0.467 to 0.876, p=0227) Health transition: 0.424 (0.180 to 0.669, p=0.551) *Subscales* *of SF-36 v2 for failure to recover at 1 week* Physical function: 0.771 (0.594 to 0.947, p=0.061) Role physical: 0.717 (0.531 to 0.903, p=0.133) Bodily pain: 0.829 (0.681 to 0.977, p=0.009), 0.90, 0.58, 2.2, 0.17 Role emotional: 0.875 (0.699 to 1.00, p=0.009), 0.90, 0.58, 2.2, 0.17 Vitality: 0.792 (0.630 to 0.953, p=0.043), 0.88, 0.58, 2.1, 0.20 Social function: 0.683 (0.438 to 1.00, p=0.204) Mental health: 0.742 (0.483 to 1.00, p=0.094) General health: 0.758 (0.550 to 0.967, p=0.073) Health transition: 0.242 (0.00 to 1.00, p=0.073)	Differential importance of SF-36 subscales for varying levels of disease severity (different set of subscales was found to predict failure to recover at 1 day vs. 1 week). Role emotional subscale was found to be significantly and robustly predictive of recovery at 1 week, in addition to vitality and bodily pain.

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Objectives	Case definition	Study design/outcome measures
Davenport, *et al.,* 2011[46] "Diagnostic accuracy of symptoms characterizing chronic fatigue syndrome"	To determine the diagnostic accuracy for single symptoms and clusters of symptoms to distinguish between individuals with and without CFS; specifically to look at recovery duration after standardized exercise challenge, single PEM symptoms and clusters of PEM symptoms to predict presence of CFS.	CDC (Fukuda, 1994)	Each subject completed 2 maximal cardiopulmonary exercise tests approximately 24 hours apart. **Procedures:** pedaling for <1 min, then workload was increased 14 watts/min until voluntary exhaustion. **Outcomes:** 7 days after the cardiopulmonary exercise test, each subject completed a questionnaire with open-ended questions: how they felt immediately after the exercise test, how they felt the next day and how long it took them to recover from the test; also asked to describe symptoms they may have experienced as a result of the test.
Gaab, *et al.,* 2004[42]	To assess the associations between psychological morbidity, symptoms severity , CFS duration and the extent of neuroendocrine dysregulations in CFS patients using a centrally acting stress paradigm.	CDC (Fukuda, 1994) and Oxford (Sharpe, 1991)	Insulin tolerance test performed at 9am after overnight fast: measures of glucose , ACTH, plasma total cortisol and salivary free cortisol collected at 20, 30, 45, 60, 90, and 120 minutes after injection of insulin (0.15U/kg H-insulin). German translation of the Fatigue Scale (Chalder, 1993).

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Total N/populations	Eligibility criteria/recruitment methods	Statistical methods
Davenport, *et al.,* 2011[46] "Diagnostic accuracy of symptoms characterizing chronic fatigue syndrome"	30; 16 with CFS and 14 non-disabled sedentary controls. United States; 100% female.	**Inclusion:** Subjects meeting CDC (Fukuda, 1994) criteria, history of fatigue lasting >6 months, unexplained by another physical, or psychological health condition. **Exclusion:** NR **Recruitment:** Convenience sample. Controls were non-disabled sedentary individuals (exercising to the point of perspiration one time per week or less). Effort made to match CFS and control subjects on sex, age and BMI.	Descriptive statistics, paired t-tests, chi-square, sensitivity/specificity, ROC curve analysis for AUC.
Gaab, *et al.,* 2004[42]	42; 21 patients with CFS and 21 healthy controls. Germany; 43% female.	**Inclusion:** Fulfillment of symptom requirements listed in postal questionnaire containing CDC (Fukuda, 1994) and Oxford (Sharpe, 1991) requirements. **Exclusion:** Medical or psychiatric diagnosis defined as exclusion criterion by CDC (Fukuda, 1994) criteria. **Recruitment:** Patients contacted through German self-help organization and screened for inclusion via postal questionnaire.	chi-square, ANOVA/ANCOVA, Pearson correlations, AUC.

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Findings	Conclusions
Davenport, *et al.,* 2011[46] "Diagnostic accuracy of symptoms characterizing chronic fatigue syndrome"	No difference between groups in terms of cardiopulmonary exercise test duration. At 1-week followup, 93% of controls reported full recovery within 24 hours vs.25% of the CFS subjects. ROC AUC for failure to recover within 1 day: 0.864, p=0.001 ROC AUC for failure to recover within 7 days: 0.598, p=0.371 ≥3 symptoms: AUC 0.871 (p=0.001; 95% CI 0.717 to 1.00), sensitivity: 0.93, specificity: 0.81, +LR 4.5; -LR 0.09 a final model including prioritized variables (according to logistic regression) included immune dysfunction, sleep disturbance, and pain: this model predicts 88% of CFS subjects and 92% of control subjects accurately **AUC (95% CI), sensitivity, specificity, positive likelihood ratio, negative likelihood ratio** *Diagnostic accuracy of individual symptoms* Fatigue: 0.750 (0.564 to 0.936, p<0.05), 0.70, 1.0, --, 0.30 Muscle stiffness: 0.603, (0.397 to 0.808, p=NR), 0.64, 0.56, 1.5, 0.64 Autonomic dysfunction: 0.643, (0.442 to 0.843, p=NR), 0.27, 0.58, 0.64, 1.3 Neuroendocrine dysfunction: 0.808, (0.645 to 0.971, p<0.01), 0.92, 0.72, 3.3, 0 Immune dysfunction: 0.719, (0.533 to 0.904, p<0.05), 1.0, 0.61, 2.6, 0 Pain: 0.772, (0.597 to 0.947, p<0.01), 0.85, 0.71, 2.9, 0.21 Sleep disturbance: 0.839, (0.687 to 0.992, p<0.01), 0.92, 0.76, 3.8, 0.11 Other: 0.487, (0.276 to 0.697, p=NR) , 0.50, 0.41, 0.85, 1.2	The optimal number of PEM symptoms is ≥3 to distinguish between CFS and control subjects.
Gaab, *et al.,* 2004[42]	AUC of the ACTH response vs. duration of CFS: -0.69, p=0.005 AUC of the ACTH response vs. Chalder fatigue scale total score: -0.41, p=0.045 AUC of the ACTH response vs. HADS depression scale: -0.53, p=0.014 AUC of the ACTH response vs. HADS anxiety scale: -0.63, p=0.003 AUC of the ACTH response vs.SIP-8 total score: 0-0.29, p=0.12 AUC of the plasma cortisol response vs. duration of CFS: 0.10, p=0.34 AUC of the plasma cortisol response vs. Chalder fatigue scale total score: 0.11, p=0.34 AUC of the plasma cortisol response vs. HADS depression scale: 0.09, p=0.36 AUC of the plasma cortisol response vs. HADS anxiety scale: -0.12, p=0.32 AUC of the plasma cortisol response vs.SIP-8 total score: -0.38, p=0.32 AUC of the salivary free cortisol response vs. duration of CFS: -0.06, p=0.41 AUC of the salivary free cortisol response vs. Chalder fatigue scale total score: 0.12, p=0.32 AUC of the salivary free cortisol response vs. HADS depression scale: 0.31, p=0.11 AUC of the salivary free cortisol response vs. HADS anxiety scale: 0.15, p=0.27 AUC of the salivary free cortisol response vs.SIP-8 total score: 0.32, p=0.09	CFS patients had reduced integrated ACTH response to insulin challenge. Cortisol responses were normal in CFS patients. Concurs with theory of deficient corticotrophin releasing hormone secretion and compensatory up-regulation of adrenal sensitivity among CFS patients.

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Objectives	Case definition	Study design/outcome measures
Gaab, *et al.,* 2002[43]	To explore alterations in negative feedback control of the HPA axis in patients with CFS.	CDC (Fukuda, 1994)	Salivary cortisol measured on 3 consecutive days: waking, and 15, 30, 45, and 60 minutes thereafter; also 8am, 11am, 3pm, and 8pm. All subjects completed visual analog scale for pain and fatigue, MFI-20, SIP-8, HADS, BDS and SCL-90R before during and after the sampling dates.
Gaab, *et al.,* 2005[44]	To assess the LPS-induced production of pro-inflammatory cytokines before and after a standardized psychological stress test in CFS patients and healthy controls and relate these finding to HPA responses and general fatigue syndromes.	CDC (Fukuda, 1994) and Oxford (Sharpe, 1991)	ACTH, plasma cortisol, salivary cortisol, differential blood count, IL-6 and TNF-alpha (baseline, and 10, 60 minutes after the TSST) German translation of the Fatigue Scale (Chalder 1993), SIP-8, SCL-90R, HADS All subjects underwent the TSST: after basal blood and saliva samples were taken they were told to prepare for a fake job interview, then given a mental arithmetic task in front of an audience and told they would be videotaped for further analysis of their behavior.

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Total N/populations	Eligibility criteria/recruitment methods	Statistical methods
Gaab, *et al.,* 2002[43]	35; 18 CFS patients and 17 controls. Germany; 52% female.	**Inclusion:** Fulfillment of symptom requirements listed in postal questionnaire containing CDC (Fukuda, 1994) and Oxford (Sharpe 1991) requirements, acute onset of CFS, ages 30-50 years, no current use of antidepressant, anziolytic, antibiotic, antihypertensive, or steroid. **Exclusion:** Medical or psychiatric diagnosis defined as exclusion criterion by CDC (Fukuda, 1994) criteria, cause for chronic fatigue on routine laboratory testing, thyroid hormone levels indicative of hypofunction and primary adrenal insufficiency. **Recruitment:** Patients contacted through German self-help organization and screened for inclusion via postal questionnaire. Patients were matched for age and sex with 21 healthy volunteer control subjects, randomly recruited by telephone.	Repeated measures ANOVA. Used log-transformed cortisol values because they were not normally distributed. AUC(total) calculated using trapezoidal method relative to baseline.
Gaab, *et al.,* 2005[44]	41; 21 CFS patients and 20 controls. Germany; 43% female.	**Inclusion:** Fulfillment of symptom requirements listed in postal questionnaire containing CDC (Fukuda, 1994) and Oxford (Sharpe, 1991) requirements, acute onset of CFS, ages 30-50 years, no current use of antidepressant, anziolytic, antibiotic, antihypertensive, or steroid. All patients medically examined by the same physician, and interviewed by a trained psychologist. **Exclusion:** Medical or psychiatric diagnosis defined as exclusion criterion by CDC (Fukuda, 1994) criteria, cause for chronic fatigue on routine laboratory testing. **Recruitment:** Patients contacted through German self-help organization and screened for inclusion via postal questionnaire. Patients were matched for age and sex with 21 healthy volunteer control subjects, free of medication, randomly recruited by telephone.	AUC calculated using trapezoidal method

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Findings	Conclusions
Gaab, *et al.,* 2002[43]	There was no difference in the AUC for awakening salivary cortisol on days 1 and 2 for CFS group vs. control. The decrease in salivary cortisol was lower for all subjects after administration of dexamethasone; with a stronger decrease in patients with CFS:12.16, p=0.003 AUC for awakening cortisol on day 3 for CFS subjects vs. controls: 6.6 (0.9) vs.23.4 (5.2), F=22.43, p<0.000. AUC for circadian cortisol profile on day 3 for CFS subjects vs. controls: 5.67 (0.9) vs.11.67 (1.5), F=10.60, p=0.002. All subscales of the MFI-20, HADS, SCL-90R and SIP-8 were significantly different for CFS subjects vs. controls. See table in paper for subscales; totals reported here: MFI-20 F=67.5, P<0.000 HADS: F=24.6, p<0.000 SCL-90R: F=27.5, p<0.000 SIP-8 F=12.81, p<0.000	CFS subjects show normal increases in salivary free cortisol after awakening and exhibit an almost similar circadian salivary cortisol profile. After administration of 0.5 mg of dexamethasone at 11pm, both salivary free cortisol profiles were suppressed in both groups; but in CFS group they remained suppressed for the entire day.
Gaab, *et al.,* 2005[44]	The HADS, SCL-90R and SIP-8 scores were all significantly higher in the CFS group AUC for IL-6 vs. Chalder fatigue scale total score: CFS 0.46, p=0.02; control 0.18, p=0.22 AUC for IL-6 vs. Chalder fatigue scale mental fatigue: CFS 0.26, p=0.13 vs. control 0.16, p=0.25 AUC for IL-6 vs. Chalder fatigue scale physical fatigue: CFS 0.51, p=0.01 vs. control 0.19, p=0.21 AUC for TNF-alpha vs. Chalder fatigue scale total score: CFS 0.60, p=0.002 vs. control 0.16, p=0.25 AUC for TNF-alpha vs. Chalder fatigue scale mental fatigue: CFS: 0.40, p=0.04 vs. control 0.16, p=0.25 AUC for TNF-alpha vs. Chalder fatigue scale physical fatigue: CFS: 0.58, p=0.003 vs. control 0.16, p=0.25	CFS patients had significantly reduced ACTH response in the psychosocial stress test, not followed by a similar different in cortisol parameters. CFS patients had an inverted pro-inflammatory cytokine response to stress compared to controls. This confirms prior reports - decreased NF-kB activity in response to stress could be a possible intracellular mechanism to mediate the assumed increase glucocorticoid sensitivity.

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Objectives	Case definition	Study design/outcome measures
Jason, *et al.,* 2011[41]	To identify the most appropriate SF-36 subscales for differentiating CFS patients.	CDC (Fukuda, 1994) SF-36	ROC curve analysis including AUC.
Jason, *et al.,* 2010[40]	To evaluate the CDC Empiric CFS definition (Reeves et al., BMC Medicine 2005) which assesses 3 areas: disability SF-36), fatigue (MFI-20) and symptoms (CDC symptom inventory). Aim to determine specific instruments and cutoffs to facilitate a more reliable approach to assessment of CFS.	Diagnosis of CFS made by dual rating by physicians, with review by 3rd if any disagreement. Based on medical history and physical examination (including 18 point fibromyalgia evaluation), SCID, and laboratory evaluation. Used refinement of Fukuda, 1994 as recommended by International Research group and the CDC (Reeves, Lloyd et al BMC health services research volume 3, 2003).	Compares MFI-20 vs. SF-36 vs. CDC symptoms Inventory

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Total N/populations	Eligibility criteria/recruitment methods	Statistical methods
Jason, *et al.,* 2011[41]	193; 2 populations: 1) 114 recruited from tertiary care and 2) 32 community based sample with 47 in a non-fatigued control group. United States; 58% female.	*Tertiary care sample* **Inclusion:** Participants ages ≥18 years, not pregnant, able to read and speak English, and physically capable of attending the sessions. CFS diagnosis according to CDC (Fukuda, 1994) criteria. **Exclusion:** Exclusionary psychiatric diagnoses according to CDC (Fukuda, 1994) criteria. **Recruitment:** 114 patients recruited from physician referrals, newspaper advertisements, and CFS support groups; they were administered a structured clinical interview and medical/laboratory evaluation. *Community sample* **Inclusion:** Self report of chronic fatigue and the concurrent occurrence of ≥4 core symptoms listed in CDC (Fukuda, 1994) case definition. 408 with chronic fatigue and symptoms that met the Fukuda CFS case definition by self-report. (Therefore termed, "CFS-like"; Of these 166 completed a structured psychiatric interview; 2 independent rates from a team of 4 physicians and a psychiatrist used Fukuda criteria to rate each patient's file.) **Exclusion:** Exclusionary medical or psychiatric conditions detected in evaluation. **Recruitment:** Of 18,675 interviewees in a community-based prevalence survey (stratified random sample of adults ages >18 years from several neighborhoods in Chicago). The control group was randomly selected from those who screened negative.	ROC curve analysis with AUC
Jason, *et al.,* 2010[40]	213 adults from community based sample from neighborhoods in Chicago (see above). Final sample n= 10824 who had CFS and 84 who did not. United States; female NR.	**Inclusion**: Self report of chronic fatigue and the concurrent occurrence of ≥4 core symptoms listed in CDC (Fukuda, 1994) case definition. 408 with chronic fatigue and symptoms that met the Fukuda CFS case definition by self-report (Therefore termed, "CFS-like"; Of these 166 completed a structured psychiatric interview; 2 independent rates from a team of 4 physicians and a psychiatrist used Fukuda criteria to rate each patient's file.) **Exclusion:** Exclusionary medical or psychiatric conditions detected in evaluation. **Recruitment:** Of 18,675 interviewees in a community-based prevalence survey (stratified random sample of adults ages >18 years from several neighborhoods in Chicago).	ROC analysis with AUC.

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Findings	Conclusions
Jason, *et al.,* 2011[41]	Community-based sample (cases vs. controls) AUC (SE) by subscale of SF-36 Vitality: 0.88 (0.04) Social functioning: 0.87 (0.04) Role-physical: 0.86 (0.04) Bodily pain: 0.85 (0.04) Physical Functioning: 0.84 (0.05) General Health: 0.80 (0.05) Mental Health: 0.75 (0.06) Role-Emotional: 0.67 (0.07) Tertiary care-based sample (cases vs. community controls) AUC (SE) by subscale of SF-36 Vitality: 0.91 (0.03) Social functioning: 0.87 (0.04) Role-physical: 0.91 (0.03) Bodily pain: 0.86 (0.04) Physical Functioning: 0.87 (0.04) General Health: 0.91 (0.35) Mental Health: 0.71 (0.05) Role-Emotional: 0.63 (0.05)	SF-36 subscales of vitality, social functioning, and role-physical have the best sensitivity and specificity and AUC thresholds. Note: this paper also cites discrimination by SF-36 subscales based on literature review included in this paper but not the focus of the paper (9 studies reported SF-36 subscales comparing CFS patients and a non-ill control group).
Jason, *et al.,* 2010[40]	**AUC, sensitivity, specificity** *MFI-20 subscale* General fatigue: 0.69, 74%, 39% Reduced activity: 0.64, 74%, 50% Meeting Reeves fatigue criteria: 0.61, 95%, 27% *CDC Symptom Inventory* Meeting Reeves core symptoms criteria (total): 0.69, 59%, 73% *SF-36 subscale* Physical functioning: 0.60, 68%, 51% Role physical: 0.66, 82%, 51% Social functioning: 0.62, 74%, 35% Role emotional: 0.57, 73%, 44% *Meeting Reeves substantial reductions criteria:* 0.56, 96%, 17% *Meeting Reeves CFS criteria:* 0.70, 65%, 76%	CDC empirical CFS definition identified approximately 65% of those with CFS. "When diagnostic tests lack reliability and accuracy, the quality of treatment and clinical research can be significantly compromised."

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Objectives	Case definition	Study design/outcome measures
Hadzi-Pavlovic, *et al.,* 2000[39]	To develop and evaluate the SOFA/CFS instrument for identifying CFS.	Met clinical criteria for CFS, recruited for another study - Lloyd, et al., 1990; also diagnostic confidence rating assigned with consensus between investigator and patient's physician.	General Health Questionnaire 5 items from the Zung depression Scale Chronic Fatigue Symptoms Checklist Somatization Checklist (39 physical symptoms)
Linder, *et al.,* 2002[38]	To investigate different approaches to establish sets of clinical classification criteria to distinguish CFS from systemic lupus erythematosus and fibromyalgia. Used self-learning artificial neural network to general diagnostic criteria sets for CFS, and vs. traditional classification criteria.	Oxford (Sharpe, 1991)	All 198 subjects were randomly assigned to 1 of 2 groups for development and validation (group A n=158 and group B n=40)
Tiev, *et al.,* 2003[37]	To determine if high ratio of Rnase L isoforms identify CFS subjects.	CDC (Fukuda, 1994)	MFI-20 administered to both groups. All had Rnase L isoform ratio measured from PBMC's.

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Total N/populations	Eligibility criteria/recruitment methods	Statistical methods
Hadzi-Pavlovic, *et al.,* 2000[39]	Final n=613, plus 430 CFS-controls, and 1,593 primary care attenders. United Kingdom; 66%.	**Inclusion:** Patients with CFS diagnosis. **Exclusion:** Patients who did not have complete data, those who did not report any current fatigue, those for whom a diagnostic confidence rating was unavailable, and those whos diagnostic confidence rating suggested that the original diagnosis of CFS was unreliable. **Recruitment:** 770 subjects with initial clinical diagnosis of CFS were sent followup questionnaire; 624 responded; 613 had usable data. Of those, 368 met final inclusion criteria for CFS. Each CFS subject gave a questionnaire to non-CFS acquaintance (452) and 430 for control. In addition, 1,593 consecutive attenders at primary care completed the self-report scales	Latent class analysis, ROC curves.
Linder, *et al.,* 2002[38]	198; 99 CFS, 41 systemic lupus erythematosus, 58 fibromyalgia. Germany; 68% female.	**Inclusion:** Patients with the leading symptom of severe fatigue >6 month duration, where known medical causes for fatigue had been excluded. **Exclusion:** Known medical causes for fatigue, primary psychiatric disorders. **Recruitment**: Patients were recruited from an outpatient population by the study physicians using a predefined standardized examination procedure. Patients with systemic lupus erythematosus and fibromyalgia who also presented with fatigue were also recruited as a comparison group.	Compared 4 methods to develop criteria sets for the classification of CFS: a) traditional non-weighted use of classification criteria, b) the weighting of criteria with regression coefficients, c) regression tree analysis, and d) an artificial neural network (back procrastination method).
Tiev, *et al.,* 2003[37]	11; 6 women and 5 men plus 14 healthy controls. France; 64% female.	**Inclusion:** Patients fulfilling CDC (Fukuda, 1994) criteria. **Exclusion**: NR **Recruitment:** NR Control group consisted of 14 matched healthy volunteers.	Using 0.4 as the cutoff for Rnase L isoform ratio.

Appendix G1. Evidence Table of Included Studies of Methods Used to Diagnosis ME/CFS

Author, year	Findings	Conclusions
Hadzi-Pavlovic, *et al.,* 2000[39]	Initial phase: clinical sample and their selected controls. 10 items with highest loadings on the first factor - total score of these 10 items. **Sensitivity, specificity** A cut-off score of 1/2 classified 341/368 CFS cases and 409/430 control subjects correctly: 93%, 95% Kraemer's QROC: 87%, 89% Including the 69 CFS subjects who had a diagnosis other than CFS or for whom there was low confidence in the diagnosis as "non-cases" did not change the sensitivity, but reduced the specificity to 83% QROC: 86%, 65% *LCA performed on 368 CFS subjects only* **Sensitivity, specificity** Cut-off of ≥2: 3 class: 100%, 90% 4 class: 97%, 98% Cut-off of ≥3: 3 class: 81%, 100% 4 class: 66%, 100%	Recommend SOFA/GP instrument with cutoff score ≥3 to maximize specificity. Longitudinal LCA analysis indicates that symptoms constructs are identifiable cross-sectionally by the SOFA/GP, and that they are stable over time.
Linder, *et al.,* 2002[38]	**Sensitivity, specificity, accuracy** *Applied traditional CDC (Holmes, 1988) definition (group A):* 62.6%, 93.9%, 78.3% *Traditional format classification criteria in validation cohort (group B):* 90.0%, 65.0%, 77.5%. Three symptoms: sudden onset of fatigue, sore throat, and impaired vision have the greatest discriminatory power in differentiating CFS from systemic lupus erythematosus and fibromyalgia. *Weighting of classification criteria with regression coefficients in validation cohort (group B):* 90.0%, 75.0%, 82.5% (optimum accuracy is obtained using sudden onset of fatigue, sore throat, and irritability (positive associations); negative associations with GI disturbances, allergies and dyspnea) *Regression tree analysis in the validation cohort (group B):* 95.0%, 80.0%, 87.5% (at most, 5 symptoms need to be ascertained before a classification can be made) *Artificial neural network in the validation cohort (group B):* 95.0%, 85.0%, 90.0% (uses 24 of the 26 symptoms)	Each method improved upon the prior methods for distinguishing CFS from systemic lupus erythematosus and fibromyalgia. The artificial neural network was superior to other methods tested. Both regression methods also led to good classification of CFS. CFS symptoms with greatest accuracy were acute onset of fatigue and sore throat.
Tiev, *et al.,* 2003[37]	Sensitivity: 91% Specificity: 71%.	In absence of infection or inflammation, a high RNase L isoform ratio could distinguish CFS subjects from healthy controls.

* = note this is one item from the questionnaire used for case definition

† = Energy quotient score calculated by dividing the perceived available energy by the amount of expended energy and multiplying by 100; if > 100 then person is outside their energy envelope.

ACTH= adrenocorticotropic hormone; am= ante meridiem; ANCOVA= analysis of covariance; ANOVA= analysis of variance; AUC= Area under the curve; bCOPE= brief coping orientation to problems experienced scale; BDS= Beck depression scale; BMC= BioMed Central; BMI= body mass index; CDC= Centers for Disease Control and Prevention; CFS= Chronic Fatigue Syndrome; CI= Confidence interval; coeff = coefficients; DSM-IV= Diagnostic and statistical manual fourth edition; GP= general practice; HADS= Hospital Anxiety and Depression Scale; HPA= hypothalamus-pituitary-adrenal axis; IL-6= interleukin - 6; kg= kilogram; LCA= latent class analysis; LPS= lipopolysaccharide; LR= likelihood ratio; MFI-20= Multidimensional fatigue inventory; mg= milligram; min = minute; n=sample size; NF-kB= nuclear factor kappa-light-chain-enhancer of activated B cells; NR= not reported; PBMC= peripheral blood derived mononuclear cell; PEM= post exertional malaise; pm= post meridiem; QROC= quality receiver operating characteristic; RCT= randomized controlled trial; Rnase L= latent Ribonuclease; ROC= receiver operating characteristic; SCID= structural clinical interview for DSM-IV; SCL-90R= symptom checklist 90-revised; SE= standard error; sens= sensitivity; SF-36= 36-item Sort Form Survey; SF-SIP-8= Sickness Impact Profile 8-item; SOFA= schedule of fatigue and anergia; spec= specificity; TNF= tumor necrosis factor; TSST= Trier social stress test; U= unit; vol = volume; vs.= versus.

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Objectives	Case definition	Methods/measures
Aslakson, *et al.,* 2006[52]	To Compared 38 variables in a series of latent class analyses to the Reeves 1994 case definition of ICF/CFS and CDC criteria.	Reeves, 1994 case definition of ICF/CFS and CDC (Fukuda, 1994) criteria	SF-36 Zung depression scale Used latent class analysis to compare empiric classification to the CDC (Fukuda, 1994) categories (CFS, idiopathic chronic fatigue, and nonfatigued)
Brown, *et al.,* 2013[53]	To compare the ME International Consensus (Carruthers, 2011) criteria with the CDC (Fukuda, 1994) criteria.	CDC (Fukuda, 1994) ME International Consensus (Carruthers, 2011)	International Consensus Fukuda CFS questionnaire DSM-IV SCID interview and medical appointment to rule out other reason for symptoms SF-36 Cognitive test: Trailmaking Tests A and B from Halstead-Reitan Battery
Jason, *et al.,* 2001[54]	To compare symptom frequency and MOS-SF outcomes between patients who meet CDC (Holmes, 1988) criteria, CDC (Fukuda, 1994) criteria and those with fatigue explained by psychiatric illness.	CDC (Fukuda, 1994) CDC (Holmes, 1988)	Comparison of symptom frequency; and SF-36

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Total N/populations	Eligibility criteria/recruitment methods
Aslakson, *et al.,* 2006[52]	159 women; 51 with CFS, 55 with chronic fatigue of insufficient symptom/severity for CFS diagnosis and 53 nonfatigued controls matched by age, sex ethnicity and BMI to those with CFS	**Inclusion:** Residents of Wichita, ages 18-69 years. Women with CFS meeting the CDC (Fukuda, 1994) criteria, chronic fatigue of insufficient symptoms/severity for CFS diagnosis, nonfatigued controls matched by age, sex, ethnicity and BMI against those with CFS. Some CFS patients had comorbid depressive disorder; some met criteria for melancholia. **Exclusion:** NR Medical and psychiatric conditions considered exclusionary by CDC (Fukuda, 1994) criteria except melancholic depression. **Recruitment:** Subset of a sample recruited for the Wichita, Kansas clinical study.
Brown, *et al.,* 2013[53]	Enrolled: 114 Analyzed: 113 (1 patient excluded for missing data) Patients met CDC (Fukuda, 1994): 74 Patients met ME International Consensus (Carruthers, 2011): 39	**Inclusion:** Patients >18 years, not pregnant, able to read and speak english, capable of attending the sessions, individuals diagnosed with CFS according to the CDC (Fukuda, 1994) criteria. **Exclusion:** Persons who used wheelchairs, those who were bedridden or housebound. **Recruitment:** Participants recruited from various sources in the Chicago metropolitan area including physician referrals.
Jason, *et al.,* 2001[54]	Overall: 55 CDC (Holmes, 1988): 14 CDC (Fukdua, 1994): 18 Chronically fatigued psychiatric group: 33	**Inclusion:** Self report of chronic fatigue and the concurrent occurrence of ≥4 core symptoms listed in CDC (Fukuda, 1994) case definition. 408 with chronic fatigue and symptoms that met the Fukuda CFS case definition by self-report (Therefore termed, "CFS-like"; Of these 166 completed a structured psychiatric interview; 2 independent rates from a team of 4 physicians and a psychiatrist used Fukuda criteria to rate each patient's file.) **Exclusion:** exclusionary medical or psychiatric conditions detected in evaluation **Recruitment**: Of 18,675 interviewees in a community-based prevalence survey (stratified random sample of adults > age 18 from several neighborhoods in Chicago). The control group was randomly selected from those who screened negative.

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Findings	Conclusions
Aslakson, *et al.,* 2006[52]	Empirically derived latent class solution compares favorably against established research criteria for CFS and idiopathic chronic fatigue.	
Brown, *et al.,* 2013[53]	**CDC (Fukuda, 1994) vs. International ME (Carruthers, 2011)** *Demographics differences* Concurrent psychiatric diagnosis: 27% (20/74) vs. 62% (24/39); p<0.001 Sudden onset of illness (<1 month): 26% (19/74) vs. 44% (16/39); p=0.05 *Mean (SD) SF-36 subscales (0-100 scale, higher scores indicate better health); only significant outcomes are reported here* Physical functioning: 51.0 (22.63) vs. 36.64 (23.32); p=0.001 Bodily pain: 46.65 (21.42) vs. 27.28 (19.45); p<0.001 Vitality: 19.86 (15.26) vs. 13.85 (13.15); p=0.04 Social functioning: 45.25 (24.22) vs. 30.45 (21.99); p=0.002 *Symptom complaints more common in International ME vs. CDC* PEM: p=0.004 Neurological: memory/concentration (p=0.01), slowness of thought (p=0.001), absent mindedness (p=0.02), confusion/disorientation (p=0001), difficulty reasoning (p=0.01), forgetting what you're trying to say (p=0.001), difficulty finding the right word (p=0.002), need to focus on one thing at a time (p<0.001), frequently lose train of thought (p=0.001), trouble expressing thoughts (p>0.001), difficulty retaining information (p<0.001), difficulty recalling information (p<0.001), put words/numbers in wrong order (p=0.04), slow to react (p<0.001), attention deficit (p=0.05), poor hand-eye coordination (p=0.02). Pain: muscle pain (p<0.001), pain in multiple joints (p<0.001), headaches (p=0.02)	ME criteria appears to select a more functionally impaired and symptomatic group of individuals with regards to both physical and mental health, vs. the Fukuda criteria. Note that this study is limited in its evaluation of the complete ME criteria because the questions were not specifically designed to fulfill the ME criteria and one symptoms (susceptibility to frequent viral infections with prolonged recovery periods) could not be included because the data had been previously collected without this information.
Jason, *et al.,* 2001[54]	**CDC (Holmes, 1988) criteria vs. CDC (Fukuda, 1994) criteria vs. chronically fatigued psychiatric group** *% symptom frequency* Sore throat: 85.7 vs. 44.4 vs. 51.5; p<0.05 Lymph node pain 85.7 vs. 27.8 vs. 27.3; p<0.01 for Fukuda vs. psychiatric group All others symptoms p=NS *Mean SF-36 sub-scales scores (0-100 scale, higher scores indicate better health)* Bodily pain: 33.3 vs. 44.5 vs. 53.7; p<0.05 General health: 34.9 vs. 55.5 vs. 49.9; p<0.05 Physical health composite: 30.9 vs. 37.0 vs. 39.9; p<0.05 for Fukuda vs. psychiatric group All other subscales and composite scales p=NS *Mean degree of impairment (0-100 scale, lower scores indicate better health)* 64.1 vs. 46.5 vs. 65.6; p<0.05 for Fukuda vs. psychiatric group	Increased occurrence of sore throat and lymph node pain in the CDC (Holmes, 1988) group vs. CDC (Fukuda, 1994) group.

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Objectives	Case definition	Methods/measures
Jason, *et al.*, 2013[4]	To compare patients who met Canadian (Carruthers, 2003) criteria with CDC (Fukuda, 1994) criteria.	CDC (Fukuda, 1994) Canadian (Carruthers, 2003)	DePaul Symptom Questionnaire SF-36

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Total N/populations	Eligibility criteria/recruitment methods
Jason, *et al.,* 2013[4]	Overall: 189 DePaul Sample: 217 recruited, 189 included BioBank sample: 242 individuals in database, included: NR Newcastle sample: 100 recruited, 96 included	*DePaul sample* **Inclusion:** Patients ages 18-65 years, capable of reading and writing English, self-reported current diagnosis of CFS, ME/CFS or ME. **Exclusion:** Endorsing lifelong fatigue, exclusionary medical of psychological conditions based on CDC (Fukuda, 1994) criteria. **Recruitment:** Patients recruited from a variety of sources including internet forums, support groups, re-contacting prior study participants, contacting individuals who had previously indicated interest in study participation. Participants completed surveys. *BioBank sample* **Inclusion:** Patients >18 years, diagnosed by a licensed physician specializing in CFS, ME/CFS and ME. **Exclusion:** NR **Recruitment:** Participants were recruited by the CFIDS Association of America through their website, social networking, internet forums and physician referral. *Newcastle sample* **Inclusion:** Patients ages 18-65 years, capable of reading and writing English, referred by physician for suspected diagnosis of CFS, ME/CFS or ME. **Exclusion:** Morbid obesity, endorsing lifelong fatigue **Recruitment:** participants were identified by primary care physicians who referred patients with a suspected diagnosis of CFS for a complete medical assessment at the Newcastle-upon-Tyne Royal Victoria Infirmary clinic.

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Findings	Conclusions
Jason, *et al.*, 2013[4]	**CDC (Fukuda, 1994) vs. Canadian (Carruthers, 2003)** *Mean (SD) SF-36 subscales (0-100 scale, higher scores indicate better health); only significant outcomes are reported here* DePaul sample Physical functioning: 35.6 (19.6) vs. 28.1 (17.9); p<0.05 Bodily pain: 59.3 (24.3) vs. 36.6 (19.7); p<0.001 BioBank sample Physical functioning: 46.8 (22.9) vs. 33.2 (21.6); p<0.001 Bodily pain: 60.0 (24.8) vs. 41.1 (21.0); p<0.001 General health: 29.8 (17.8) vs. 22.8 (14.2); p<0.01 Social functioning: 42.7 (28.8) vs. 24.0 (21.6); p<0.001 Mental health: 72.2 (13.7) vs. 66.0 (19.6); p<0.05 Vitality: 20.6 (13.7) vs. 12.0 (12.3); p<0.001 Newcastle sample Physical functioning: 49.1 (25.8) vs. 29.6 (25.4); p<0.05 Bodily pain: 45.2 (25.0) vs. 29.5 (21.3); p<0.05 General health: 35.3 (18.9) vs. 20.7 (12.5); p<0.01 Social functioning: 39.4 (20.9) vs. 25.0 (20.5); p<0.05 *Symptom complaints more common in Canadian (Carruthers, 2003) vs. CDC (Fukuda, 1994); p<0.05 for those noted below.* PEM: 3/5 subcategories in all 3 samples; 4/5 in DePaul and Solve samples Sleep parameters (unrefreshing sleep): 1/6 in all 3 samples; 3/6 other sleep parameters in DePaul and Solve samples only Pain: 5/7 subcategories in all 3 samples, 7/7 in DePaul and Solve samples Neurocognitive: 4/13 in all 3 samples; 15/15 in DePaul and Solve samples Autonomic: 4/7 in all 3 samples, 7/7 in DePaul and Solve samples Neuroendocrine: 5 /10 in all 3 samples; 10/10 in DePaul and Solve samples Immune: 4/5 in all 3 samples; 5/5 in DePaul and Solve samples	

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Objectives	Case definition	Methods/measures
Jason, *et al.,* 2012[40]	To compare the Canadian (Carruthers, 2003) criteria to the CDC (Fukuda, 1994) criteria, and other ME case definitions.	CDC (Fukuda, 1994) Canadian (Carruthers, 2003) Revised Ramsay, 1988	CFS questionnaire (validated by Jason 1997) to assess symptoms, with modified scoring system ranging from 0-100 with higher scores indicating more impairment DSM-IV SCID interview, medical, and neurological history and exam, other explanation for CFS-like symptoms CFS Questionnaire (Komaroff 1996) to rule out other disorders MOS-SF Cognitive test: Trailmaking Test Parts A and B Heart rate lying down, 2 minutes after standing, and 10 minutes after standing Used symptom counts, chi-square and MANOVA to assess differences between group

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Total N/populations	Eligibility criteria/recruitment methods
Jason, *et al.,* 2012[40]	114 meeting Fukuda criteria for CFS (24 individuals were screened and then excluded for alternative diagnosis or not meeting criteria (<4 Fukada symptoms)	**Inclusion:** Patients >18 years, not pregnant, able to read and speak english, capable of attending the sessions, individuals diagnosed with CFS according to the CDC (Fukuda, 1994) criteria. **Exclusion:** Persons who used wheelchairs, those who were bedridden or housebound. **Recruitment:** Participants recruited from various sources in the Chicago metropolitan area including physician referrals.

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Findings	Conclusions
Jason, *et al.,* 2012[40]	Of 114 people meeting Fukuda CFS criteria, 56 did not meet the ME/CFS criteria and 97 did not meet the ME criteria (56 were classified as ME/CFS and 27 as ME). 1 person was unable to be categorized. **ME/CFS vs. CFS not ME/CFS** *Demographics differences* Disability: 32% (18/57) vs. 16% (9/56); p=0.06 Current psychiatric diagnoses: 58% (33/57) vs. 20% (11/56); p=0.05 Sudden illness onset (<1 month): 41% (22/57) vs. 24% (13/56); p=0.0 Physical cause of fatigue: 64% (36/57) vs. 65% (35/56); p=0.04 *Mean (SD) SF-36 subscales (0-100 scale, higher scores indicate better health); only significant outcomes are reported here* Physical functioning: 38.0 (21.9) vs. 53.8 (23.4); p=0.00 Bodily pain: 32.2 (20.0) vs. 48.0 (22.1); p=0.00 General health: 28.5 (16.0) vs. 36.5 (18.3); p=0.02 Vitality: 14.8 (12.0) vs. 20.9 (16.6); p=0.02 Social functioning: 34.0 (22.7) vs. 46.6 (24.2); p=0.01 *Symptom complaints more common among ME/CFS vs. CFS not ME/CFS* Fatigue: p=0.00; PEM: p=0.00; unrefreshing sleep: p=0.00; need to nap each day: p=0.05; difficulty falling asleep: p=0.01; all pain parameters (muscle pain, pain in multiple joints, headaches, chest pain, abdomen pain, eye pain): all p<0.02; all neurological parameters (impaired memory and concentration, abnormal sensitivity to light, slowness of thought, confusion/disorientation, difficulty finding the right work, difficulty comprehending information, need to have focus on one thing at a time): p=0.00; all autonomic parameters (racing heart, shortness of breast, dizziness, feel unsteady on feet): p<0.01; and tender/sore lymph nodes: all p=0.00 *Symptom complaints more common among ME vs. CFS not ME/CFS* Headaches: p=0.05; chest pain: p=0.04; abdomen pain: p=0.00; eye pain: p=0.00; difficulty finding the right word: p=0.05; need to have focus on one thing at a time: p=0.02; all autonomic parameters (racing heart, shortness of breast, dizziness, feel unsteady on feet): all p<0.02; tender/sore lymph nodes: p=0.02; and hot/cold spells: p=0.05 **ME/CFS vs. CFS not ME/CFS; ME vs. CFS not ME** Mean (SD) heart rate (bpm) Lying down: 80.7 (14.8) vs. 74.5 (11.1); p=0.02; 84.4 (16.4) vs. 75.4 (11.4); p=0.00 Standing 2 minutes: 94.2 (17.1) vs. 85.7 (14.6); p=0.00; 96.9 (18.9) vs. 87.7 (14.9); p=0.00 Standing 10 minutes: 94.6 (14.5) vs. 86.2 (13.6); p=0.00; 97.8 (14.4) vs. 88.1 (13.9); p=0.00 Mean (SD) Trailmaking test scores A-time: 32.9 (13.6) vs. 26.8 (9.9); p=0.02; 35.3 (15.8) vs. 28.2 (10.3); p=0.02 B-time: 56.1 (25.1) vs. 46.8 (14.9); p=0.03; 61.2 (28.3) vs. 48.5 (17.3); p=0.00 Symptoms and Psychiatric Comorbidity: ME/CFS group had 7.3 of the 13 Kroenke (2003) symptoms vs 5.1 for Fukuda CFS (p<0.05); ME group had 8.1 of the 13 Kroenke (2003) symptoms vs 5.6 for Fukuda CFS (p<0.01).	ME and the Canadian ME/CFS criteria appears to select patients who have more severe functional impairment, physical and cognitive symptoms than the Fukuda CFS criteria. ME/CFS criteria appears to identify more impairments in symptoms, whereas the ME criteria appears to identify impairment in functional status. No significantly different rates of psychiatric illness for ME vs. Fukuda CFS; and no difference on the SF-36 role emotional and mental health scales for ME vs Fukuda CFS. ME group had more Kroenke symptoms than Fukuda CFS; ME/CFS had fewer differences at the 0.01 level vs. Fukuda CFS.

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Objectives	Case definition	Methods/measures
Katon, *et al.,* 1991[55]	To identify psychiatric differences between patients with chronic fatigue and those with rheumatoid arthritis, and to investigate whether patients meeting the CDC (Holmes, 1988) criteria can be differentiated from patients with chronic fatigue on measures of disability and psychosocial distress.	CDC (Holmes, 1988)	General Health Questionnaire total score MOS-SF Modified Somatic Perception Questionnaire Pennebaker inventory of Limbic Languidness
Komaroff, *et al.,* 1996[56]	To measure functional status and well-being of patients with CFS vs. general population and 6 disease comparison groups.	CDC (Fukuda, 1994)	SF-36

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Total N/populations	Eligibility criteria/recruitment methods
Katon, *et al.,* 1991[55]	79 with chronic fatigue; 19 with CFS; 31 with rheumatoid arthritis	**Inclusion:** Physician or self referred for CFS. Controls were RA patients. **Exclusion:** NR **Recruitment**: Subjects referred by community PCP or self-referred. 31 consecutive RA patients recruited from rheumatology clinic (all meeting ACR criteria).
Komaroff, *et al.,* 1996[56]	223 with CFS recruited from CFS clinic; 2,474 population-based control sample; and chronic disease comparison group (2,089 with HTN, 216 with CHF, 163 with DM, 107 with acute MI, 107 with MS, and 502 with depression)	**Inclusion:** Patients who fully met the CDC (Holmes, 1988) criteria and seen since 1990. **Exclusion:** NR **Recruitment:** CFS patients drawn from an NIH-supported CFS Cooperative Research Center at Brigham and Women's Hospital and Harvard Medical School. General population comparison came from SF-36 administered as part of National Survey of Functional Health Status. Disease comparison groups came from a group who had SF-36 administered as part of the Medical Outcomes Study (MOS) and others seen at the Brigham & Women's Hospital ambulatory practices.

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Findings	Conclusions
Katon, *et al.,* 1991[55]	**CFS vs. RA** *GHQ scores* Mean (SD) total score: 12.5 (8.0) vs. 5.1 (4.6); p<0.001 Score of ≥11: 53% (47/98) vs. 13% (3/31); p<0.001 *Mean (SD) MOS-SF (1-100 scale, higher score indicates better health); significant results only reported here* Mental health: 17.7 (5.5) vs. 23.0 (5.4); p<0.01 Health perception: 3.4 (1.4) vs. 5.3 (2.1); p<0.001 No significant difference for SF-36 physical function and role functional, Modified Symptoms Perception Questionnaire, or the Pennebaker Inventory of Limbic Languidness.	
Komaroff, *et al.,* 1996[56]	**Significant p values for means on SF-36 subscales: comparisons vs. CFS** Physical functioning: p<0.00001 general population, HTN, DM, AMI, and depression; p=0.00004 CHF Role physical: p<0.00001 all Bodily pain: p<0.00001 all General health: p<0.00001 all Vitality: p<0.00001 all but MS which was NS (p=0.1369) Social functioning: p<0.00001 Role emotional: p<0.00001 general population, HTN, DM, and depression; p=0.3918 CHF; p=0.1077 MS Mental health: p<0.00001 all but MS which p=0.0005	

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Objectives	Case definition	Methods/measures
Lewis, *et al.,* 2013[57]	To compare clinical and autonomic features of CFS in patients >50 years to those age 16-20 years.	CDC (Fukuda, 1994)	Heart rate variability Baroreceptor sensitivity FIS CFQ HADS, HADS-A and HADS-D SF-36 Chalder fatigue scale ESS OGS - 5 items, each graded 0-4 t-tests statistics
Van Hoof and De Meirleir, 2005[58]	To compare ME and CFS regarding cognitive problems and functionality using standardized objective test batteries.	CDC (Fukuda, 1994) London criteria for ME (National Task Force, 1994)	SF-36 MFI-20 KPS Exercise

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Total N/populations	Eligibility criteria/recruitment methods
Lewis, *et al.,* 2013[57]	179 subjects recruited; study sample includes 25 subjects >50 years matched by sex and length of history for 25 CFS subjects ages 16-29 years	**Inclusion:** Attending the clinic between November 2008 and June 2011 and diagnosed with CFS using CDC (Fukuda, 1994) criteria. **Exclusion:** Secondary causes for fatigue (such as hypothyroidism, diabetes), fulfilled CDC (Fukuda, 1994) exclusionary criteria. **Recruitment:** Consecutive patients attending the Northern Regional Department of Health Funded CFS Clinical Service (Newcastle upon Tyne, UK) with a diagnosis of CFS using Fukuda criteria.
Van Hoof and De Meirleir, 2005[58]	67; 41 with CFS and 26 with ME	**Inclusion:** Patients visiting the outpatient Chronic Fatigue clinic to be screened for CFS or ME and fulfilled either the CDC (Fukuda, 1994) criteria for CFS or the London criteria for ME. **Exclusion:** NR **Recruitment:** Recruited from Chronic Fatigue Clinic of the Vrije Universiteit Brussel. Recruited consecutive patients, and every second patient was enrolled.

Appendix G2. Evidence Table of Included Studies Evaluating the Accuracy and/or Concordance of Different Diagnostic Criteria

Author, year	Findings	Conclusions
Lewis, *et al.*, 2013[57]	**Age 16-29 years vs. ≥50 years; only significant results reported here** Mean (SD) BMI (kg/m^2): 22 (3) vs. 26 (3); p=0.002 Mean (SD) FIS: 85 (33) vs. 107 (27); p=0.02 Mean (SD) Chalder Fatigue severity scale (0-56 scale, lower score indicates better health): 9 (3) vs. 11 (1); p=0.002 Mean (SD) HADS-D: 7 (3) vs. 10 (4); p=0.005 Mean (SD) total SF-36 score (0-100, higher scores indicate better health): 20 (5) vs. 16 (5); p=0.03 Mean (SD) self-efficacy scores: 31 (12) vs. 22 (14); p=0.02 Mean (SD) heart rate (bpm): 80 (15) vs. 71 (8); p=0.007 Mean (SD) LVET (ms): 274.6 (16) vs. 285.8 (9); p=0.004 Mean (SD) LFnu: 51.5 (17) vs. 63.8 (18); p=0.01 Mean (SD) HFnu: 49.1 (18) vs. 36.2 (18); p=0.01 Mean (SD) LF/HF: 1.5 (0.9) vs. 2.2 (1.4); p=0.04 Mean (SD) BRS: 19.7 (12) vs. 9.9 (5); p=0.0004 Autonomic and hemodynamic differences: higher LVET (p=0.004), high LFnu (p=0.01), higher HFnu (p=0.01), higher LF/HF (p=0.04), lower BRS (p=0.0004) for the subjects > 50 vs those age 16-26. No difference in HR, systolic BP, diastolic BP, mean BP, total HRV, BEI, or systolic BP with active stand.	
Van Hoof and De Meirleir, 2005[58]	**CFS vs. ME** *Demographic differences; only significant differences reported here* Mean age (SD): 43 (10) vs. 34 (7) years; p=0.001 *Mean (SD) SF-36 subscale scores (0-100 scale, higher scores indicate better health)* Role emotional: 62 (44.05) vs. 83 (31.05); p=0.024 Mental health: 60 (17.90) vs. 69 (13.41); p=0.049 *Mean (SD) MFI-20 (4-20 scale, lower score indicates better health)* General fatigue: 18 (2.73) vs. 17 (2.88); p=0.029 *Physical parameters; only significant differences reported here* Mean (SD) age predicted heart rate (bpm): 178.04 (10.67) vs. 185.57 (6.64); p=0.049 Mean (SD) VO_2 predicted: 26.81 (3.66) vs. 29.39 (2.28); p=0.049 *Note:* Only the Role Emotional SF-36 subscale seemed able to discriminate ME patients from CFS patients. The analysis correctly classified 59.7% of the cases. 73% of the ME cases were correctly classified, and 51% of the CFS patients.	

ACR= American College of Rheumatology; AMI= acute myocardial infarction; BEI= baroreflex effective index; BMI= body mass index; BP= blood pressure; bpm= beats per minute; BRS= baroreflex sensitivity; CDC= Centers for Disease Control and Prevention; CFIDS= chronic fatigue and immune dysfunction syndrome; CFQ= cognitive failures questionnaire; CFS= chronic fatigue syndrome; CHF= congestive heart failure; DM= depressed mood; DSM-IV= Diagnostic and Statistical Manual fourth edition; ESS= Epworth sleepiness scale; FIS= fatigue impact scale; GHQ= general health questionnaire; HADS= Hospital Anxiety and Depression Scale; HADS-A= anxiety subscale of HADS; HADS-D= depression subscale of HADS; HF= high frequency; HFnu= high frequency normalized units; HR= heart rate; HRV = heart rate variability; HTN= hypertension; ICF= idiopathic chronic fatigue; kg= kilogram; KPS= Karnofsy Performance Scale; LF= low frequency; LFnu= low frequency normalized units; LVET= left ventricular ejection time; m= meter; MANOVA= multivariate analysis of variance; ME= myalgic encephalomyelitis; MFI-20= Multidimensional fatigue inventory; MI = myocardial infarction; MOS-SF= medical outcomes study short form; ms = milliseconds; MS= multiple sclerosis; NIH = National Institutes of Health; NR= not relevant; NS= not significant; OGS= orthostatic grading scale; PCP = primary care physician; PEM= post exertional malaise; RA= rheumatoid arthritis; SCID= structured clinical interview for DSM-IV; SD= standard deviation; SF-36= 36-item Sort Form Survey; UK= United Kingdom; VO_2= volume oxygen; vs.= versus

Appendix G3. Evidence Table of Included Studies of Harms of Diagnosis

Author, year	Objective	N/population	Findings
Åsbring, *et al.,* 2002[60]	To investigate whether patients with CFS and fibromyalgia experience stigma and to examine the strategies they use to avoid enacted stigma.	N=25 women (12 CFS, 13 fibromyalgia) were interviewed to the point of saturation of themes regarding stigma.	**Two main aspects of stigmatization were reported** 1) Women experienced their moral character being called into question 2) They experienced distress from being psychologized by others, especially doctors (decided in advance that problems were fictitious or psychological; and that this experience was deeply violating)
Assefi, *et al.,* 2003[61]	To examine self-reported disability in patients with CFS and fibromyalgia, subsyndromal fatigue, compared with chronically fatiguing but unrelated medical condition.	N=555 (207 CFS, 76 fibromyalgia, 87 CFS+fibromyalgia, 31 sybsyndromal fatigue, 154 medical conditions) of 630 (88%) patients from a university CFS clinic responded to a survey about financial, occupational, and personal consequences of their illness.	**Disability outcomes reported by >20% of CFS (n=207) group** Lower standard of living: 44% (92/207) Significant decrease in social life: 84% (174/207) Lost friends: 38% (79/207) Significant decrease in recreational activities: 90% (186/207) *Of those CFS patients employed (n=119)* Taking a new job requiring fewer skills: 25% (30/119) Took a substantial pay cut: 30% (35/119)
Deale, *et al.,* 2000[62]	To evaluate patient experience with psychiatric diagnoses in CFS patients; evaluate whether psychiatric illness is overdiagnoses in routine clinical practice among CFS patients.	N=68 patients met Oxford criteria (Sharpe, 1991) for CFS completed a questionnaire asking about psychiatric diagnoses or labels given during their illness and then underwent interview to assess for those psychiatric disorders with the DSM III-R.	**Reported psychiatric diagnosis** 46% (31/68) given psychiatric diagnosis (usually depression) 68% (21/31) given depression diagnosis were misdiagnosed 35% (13/37) not given psychiatric diagnosis met DSM III-R criteria for treatable psychiatric disorder, present for ≥6 months
Dickson, *et al.,* 2007[63]	To understand participants' prioritizations and understandings of CFS.	N=14 people with self-reported CFS were interviewed about living with CFS.	**Reported difficulties about living with CFS** 71% (10/14) experienced delay in getting CFS diagnosis 57% (8/14) were prescribed antidepressants for depression diagnosis instead of CFS diagnosis **Descriptive results** Participants reported that they perceived many medical practitioners to hold stereotypical views of patients with CFS, namely that disease was either psychological or indicative of an affective disorder. Problems with friends and partners centered on the fact that the patient is not visibly ill, and that the symptoms are inconsistent or variable.

Appendix G3. Evidence Table of Included Studies of Harms of Diagnosis

Author, year	Objective	N/population	Findings
Green, *et al.,* 1999[64]	To evaluate stigma among people with CFS.	N=45 of 67 (67%) initially recruited patients with CFS reported perceptions of stigma.	**Reported perceptions of stigma** 95% reported feeling estranged 70% thought others attribute their symptoms to psychological or personality 40% felt need to be secretive about their symptoms in some circumstances
Guise, *et al.,* 2010[65]	To evaluate ME/CFS sufferers' descriptions of interactions with medical professionals.	N=38 members of an internet-based ME/CFS support group were asked to comment on how they felt about the way medical people treated them.	**Descriptive results** Patients with CFS reported that health professionals lack clinical expertise and empathy; and that they encountered professionals who lacked expectation of treatability, described themselves as fortunate in terms of experiences with medical professionals, and described themselves as able to cope and actively seeking out information and treatment.
Jason and Taylor, 2001[59]	To evaluate perceptions of diagnostic labeling among medical trainees, university undergraduates and practicing mental health practitioners.	N=105 medical trainees (Study 1) N=141 undergraduate psychology students (Study 2) Randomly assigned to being told the case presented to them had CFS, Florence Nightingale Disease, or ME. The case studies were identical. N=93 mental health practitioners (Study 3) Randomly assigned to 1/3 treatments for CFS, and given identical case studies of a woman with prototypic CFS symptoms, diagnosed by a physician; treatments were 1) Ampligen - IV immune modulator, 2) CBT with graded activity, or 3) cognitive coping skills therapy.	**Studies 1 and 2: told case was CFS vs. Florence Nightingale Disease vs. ME** Correctly diagnosed: 54% vs. 19% vs. 28%; p<0.01 Disease result of as-yet-undiscovered cancer, infection or other illness: 22% vs. 47% vs. 28%; p<0.05 Reported patient was likely to improve: 41% vs. 42% vs. 16%; p<0.05 **Study 3: Data not shown** Participants assigned to Ampligen were more likely to think that the patient was correctly diagnosed as having CFS (p<0.05) and also thought the patient was significantly more disabled than did individuals in the CBT with graded activity condition (p<0.05)
Jason, *et al.,* 2001[66]	To reproduce a prior study of labeling, in term of whether different names for CFS prompts different attributions regarding cause.	N=105 medical trainees (Study 1) N=141 undergraduate psychology students (Study 2) Randomly assigned to being told the case presented to them had CFS, Florence Nightingale Disease, or ME. The case studies were identical.	**Told case was CFS vs. Florence Nightingale Disease vs. ME** Mean score of whether correct diagnosis (1-6 scale; 1=not at all and 6=very likely): 4.5 vs. 3.9 vs. 4.0; p<0.01 Proportion that associated "causal factors" with diagnosis: 28% vs. 31% vs. 49%; p<0.01 Mean score of whether diagnosis was associated "organ donorship" (1-6 scale; 1=not at all and 6=very likely): 3.7 vs. 3.5 vs. 3.1; p<0.05

CBT= cognitive behavioral therapy; CFS= chronic fatigue syndrome; DSM-III-R= Diagnostic and Statistical Manual third edition revised; ME= myalgic encephalopathy; n= sample size; vs.= versus.

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Medications				
Blacker, *et al.,* 2004[67]	RCT of oral galantamine (acetyl-cholinesterase inhibitor) at various doses vs. placebo for underlying cause	**Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo** Mean ages (years): 39 vs. 39 vs. 39 vs. 37 vs. 38 % Female: 72 (64/89) vs. 71 (61/86) vs. 62 (56/91) vs. 62 (53/86) vs. 62 (51/82) % White: 99 (88/89) vs. 92 (79/86) vs. 98 (89/91) vs. 95 (82/86) vs. 94 (77/82)	CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18-65 years, modified CDC criteria, illness duration <7 years. **Exclusion:** Concurrent DSM-IV diagnoses: major depressive disorder, psychotic disorders, panic disorder, substance misuse, somatization disorder, anorexia or bulimia nervosa, obesity, and sleep disorders; received inpatient psychiatric care had previously attempted suicide or both; irritable bowel syndrome; peptic ulcer; severe asthma; endocrine or metabolic disease; HIV; know sensitivity to cholinergic agents; possible exposure to organophosphate compounds; diagnosis of Gulf War syndrome; pregnant or lactating; women with irregular menstrual irregularities associated with fatigue.	<7 years
Blockmans, *et al.,* 2003[69]	Crossover RCT of oral hydrocortisone + fludrocortisone (corticosteroid) vs. placebo for underlying cause	Mean age: 38 years % Female: 91 (73/80) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Meet ≥4 CDC minor criteria for CFS. **Exclusion:** History of gastric or duodenal ulcer, arterial hypertension, glaucoma, or diabetes; pregnant; or incomplete screening examination.	Mean (range): 30 (16-60) months
Diaz-Mitoma, *et al.,* 2003[74]	RCT of isoprinosine (antiviral and immunomodulatory drug) vs. placebo for underlying cause	Mean age (SD): 46 (8) years % Female: 81% (13/16) % White: 100	CDC (Holmes, 1988 and Fukuda, 1994) criteria **Inclusion:** Ages 18-60 years with ongoing symptoms for ≥6 months. Females were required to have a negative pregnancy test. **Exclusion:** Malignancy, major organ or system pathology inconsistent with CFS	≥6 months

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Medications					
Blacker, *et al.,* 2004[67]	Number approached: NR Number screened: NR Number eligible: 434 Number randomized: 434 Number analyzed: 423	United Kingdom, Western Europe, United States 35 clinic centers	16 weeks (8 weeks at full dose)	**Overall:** 30% (130/434) **Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo:** 20% (18/89) vs. 36% (31/86) vs. 35% (32/91) vs. 31% (27/86) vs. 27% (22/82)	Non-compliance: 6 (4 interventions vs. 2 placebo)
Blockmans, *et al.,* 2003[69]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 100 Number analyzed: 80	Belgium Single site tertiary care university clinic	3 month treatment; 3 month placebo crossover	20% (20/100)	NR
Diaz-Mitoma, *et al.,* 2003[74]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 16 (10 isoprinosine, 6 placebo) Number analyzed: 15 (10 isoprinosine, 5 placebo)	Canada 1 Research site in Ottawa	12 weeks of treatment	6.3% (1/16, was in placebo group)	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Medications		
Blacker, *et al.,* 2004[67]	**Galantamine 7.5:** Galantamine 2.5 mg three times per day **Galantamine 15:** Galantamine 5 mg three times per day **Galantamine 22.5:** Galantamine 7.5 mg three times per day **Galantamine 30:** Galantamine 10 mg three times per day **Placebo:** Identical placebo three times per day *Note:* For intervention groups doses were titrated over 3-8 week period, starting at 2.5 mg/day with weekly increments of 2.5-7.5 mg depending on target dose, which was maintained for another 8 weeks	**Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo** *Chalder Fatigue Rating Scale least square mean change from baseline (positive changes indicate better health)* Physical: 9.25 vs. 8.77 vs. 11.02 vs. 9.99 vs. 9.86 Mental: 6.46 vs. 5.89 vs. 7.74 vs. 6.60 vs. 6.80
Blockmans, *et al.,* 2003[69]	**Hydrocortisone:** Hydrocortisone 5 mg/day + 9-alpha fludrocortisone 50 µg/day **Placebo:** Placebo	**Hydrocortisone vs. placebo** *Visual Analog Scale (0-10)* Degree of fatigue: 6.6 (2.0) vs. 6.7 (2.1); p=0.76 *Mean (SD) SFQ score (4-28, higher scores indicate better health)* : 8 (5) vs. 7 (5); p=0.69
Diaz-Mitoma, *et al.,* 2003[74]	**Isoprinosine:** 2 tablets of oral isoprinosine 500 mg TID (total=3g/day) in weeks 1, 3, 5, 7, 9, and 11 only on Monday-Friday; and once a day (total=1g/day) in weeks 2, 4, 6, 8, 10, and 12 only on Monday-Friday. **Placebo:** Identical placebo following the same schedule as the isoprinosine group.	**Isoprinosine vs. placebo** % change on KPS from baseline to 12 weeks: 0.6% (12.1) for 6 treatment group "improved" participants; 0.0% (10.7) for 4 treatment group "not improved" participants; 3.0% (6.9) for 5 placebo participants; p=0.93

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Medications		
Blacker, *et al.,* 2004[67]	**Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo;** all comparisons are NS between groups *FIQ least square mean change from baseline* Global Well Being (composite): -77.84 vs. -88.65 vs. -29.92 vs. -60.67 vs. -53.89	NR
Blockmans, *et al.,* 2003[69]	**Hydrocortisone vs. placebo** *Visual Analog Scale (0-10)* Degree of well-being: 5.0 (2.4) vs. 4.6 (2.6); p=0.14	**Hydrocortisone vs. placebo** *SF-36 (0-100 scale, higher scores indicate better health)* Physical functioning: 31.7 (18.2) vs. 30.4 (18.1); p=0.34
Diaz-Mitoma, *et al.,* 2003[74]	NR	No difference in activities of daily living scale, data not provided

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Medications		
Blacker, *et al.,* 2004[67]	NR	**Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo;** all comparisons are NS between groups *% Improved on modified CGI:* 25 (29%) vs. 18 (23%) vs. 19 (22%) vs. 16 (20%) vs. 14 (18%)
Blockmans, *et al.,* 2003[69]	NR	NR
Diaz-Mitoma, *et al.,* 2003[74]	NR	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Medications						
Blacker, *et al.,* 2004[67]	**Overall:** 23% (88/389) **Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo:** 14% (12/89) vs. 23% (20/86) vs.24% (22/91) vs. 26% (22/86) vs.15% (12/82)	Galantamine: 2% (8/389) none attributed to the study drug	Depression, nausea and headache most common in both groups	90% (389) reported adverse events; 23% (88) withdrew	Shire Pharmaceutical Development Ltd.	Fair
Blockmans, *et al.,* 2003[69]	1 acne and weight gain	None	None	1	NR	Fair
Diaz-Mitoma, *et al.,* 2003[74]	0	NR	NR	NR	Grants from Enterprise Ireland (130590/D)	Poor

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
McKenzie, *et al.,* 1998[68]	RCT of oral hydrocortisone (corticosteroid) vs. placebo for underlying cause	**Hydrocortisone vs. placebo** Mean age: 37 vs. 38 years % Female: 83 (29/35) vs. 77 (27/35) % White: 97 (34/35) vs. 94 (33/35)	CDC (Holmes, 1988) and CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18-55 years, illness began over a period 6 weeks or less. **Exclusion:** Contraindication to systemic steroids.	**Hydrocortisone vs. placebo** Mean: 47 vs. 60 months; p=0.07
Montoya, *et al.,* 2013[71]	RCT of oral valganciclovir (antiviral drug) vs. placebo for underlying cause	**Valganciclovir vs. placebo** Mean age: 50 vs. 48 years % Female: 75 (15/20) vs. 50 (5/10) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Age18 and older; suspected viral onset of CFS; elevated antibody titer meeting additional criteria. **Exclusion:** Reasons for exclusion include: low antibody titers on repeat testing, exclusionary comorbidities, conflicting medication, declined to participate.	**Valganciclovir vs. placebo** Mean: 12.7 vs. 13.5 years
Peterson, *et al.,* 1990[70]	RCT of IV IgG vs. placebo for underlying cause	Mean age: 41 years % Female: 73 (22/30) Race: NR	CDC (Holmes, 1988) criteria **Inclusion:** Diagnosis of CFS. **Exclusion:** NR	Mean: 3.8 years
Strayer, *et al.,* 1994[72]	RCT of IV rintatolimod (Ampligen=antiviral and immunomodulatory drug) vs. placebo for underlying cause	**Rintatolimod vs. placebo** Mean age: 36 vs. 35 years % Female: 64 (no. NR) vs. 85 (no. NR); p=0.003 Race: NR vs.NR	CDC (Holmes,1988) and (Fukuda, 1994) criteria **Inclusion:** CFS diagnosed ≥12 months before study; severe debilitation (KPS 20-60). **Exclusion:** Women who were pregnant or nursing.	**Rintatolimod vs. placebo** Mean: 6.1 vs. 4.4 years

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
McKenzie, *et al.,* 1998[68]	Number approached: NR Number screened: 638 Number eligible: 179 Number enrolled: 70 Number analyzed: 60-70 varied by outcome	United States Single center at the NIH	12 weeks	10% (7/70)	NR
Montoya, *et al.,* 2013[71]	Number approached: 155 Number screened: 45 Number eligible: 34 Number enrolled: 30 Number analyzed: 30 (20 valganciclovir, 10 placebo)	United States Patients referred to study at Stanford University	6 months treatment and 6 more months followup (unbinding and outcomes measured at 9 months)	1 from each group	100% at 3 weeks; 90% at 12 weeks; 65% at 24 weeks
Peterson, *et al.,* 1990[70]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 30 Number analyzed: 28	United States, Minnesota Single center	6 months	7% (2/30)	NR
Strayer, *et al.,* 1994[72]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 92 Number analyzed: 76-84 varies by outcome	United States 4 clinical sites	24 weeks	9% (8/92) 4 from each group	91% (84/92)

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
McKenzie, *et al.,* 1998[68]	**Hydrocortisone:** Oral hydrocortisone 20-30 mg every morning and 5 mg every evening (13 mg/m^2 every morning and 3 mg/m^2 every evening) **Placebo:** Placebo	**Hydrocortisone vs. placebo** *Mean Change in POMS subscales* Fatigue (negative changes indicate better health): -3.6 (5.3) vs. -1.8 (4.5); p=0.21 Vigor (positive changes indicate better health): 1.2 (3.3) vs. 0.7 (3.3); p=0.45
Montoya, *et al.,* 2013[71]	**Valganciclovir:** Oral valganciclovir 900 mg BID for 21 days, then 900 mg once daily for total of 6 months **Placebo:** Placebo	**Valganciclovir vs. placebo** *Change in MFI-20 (negative changes indicate better health)* Baseline to 9 months : -6.15 vs -1.10; p=0.224 *Change in FSS (negative changes indicate better health)* -0.06 vs 0.02; p=0.006
Peterson, *et al.,* 1990[70]	**IgG: I** IV IgG (1 g/kg) every 30 days for 6 months (6 infusions) **Placebo:** IV placebo (1% albumen solution) every 30 days for 6 months (6 infusions)	NR
Strayer, *et al.,* 1994[72]	**Rintatolimod:** IV rintatolimod 200 mg twice weekly 4 times, then 400 mg twice weekly for a total of 24 weeks **Placebo:** Placebo	**Rintatolimod vs. placebo** *Exercise duration* % change from baseline: +10.3 vs. +2.1; p=0.007 *Exercise work* % change from baseline: +11.8 vs. +5.8; p=0.011

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
McKenzie, *et al.,* 1998[68]	**Hydrocortisone vs. placebo** *Global Wellness scale (0-100)* Improvement: 20/30 (67%) vs. 19/35 (54%); p=0.31 Mean change: 6.3 (11.7) vs. 1.7 (8.8); p=0.06	**Hydrocortisone vs. placebo** *Mean change (SD) in Activity Scale (10 point scale)* 0.3 (1.1) vs. 0.7 (1.4); p=0.32
Montoya, *et al.,* 2013[71]	NR	**Valganciclovir vs. placebo** *Change in self-reported physical function (positive change indicates better health)* 1.02 vs 0.46; p=0.217
Peterson, *et al.,* 1990[70]	NR	**IgG vs. placebo** *SF-12 (0-100 scale, higher scores indicate better health)* Physical: 56.0 (23.2) vs. 51.8 (27.2); p=NS Social: 5.2 (5.5) vs. 9.4 (7.9); p<0.05
Strayer, *et al.,* 1994[72]	NR	**Rintatolimod vs. placebo** % change in *KPS score from baseline (0-100 scale, higher scores indicate better health)* +20 vs. 0; p=0.023 % change in *ADL score from baseline (0-100 scale, higher scores indicate better health)* +23.1 vs. 14.1; p=0.034

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
McKenzie, *et al.,* 1998[68]	NR	NR
Montoya, *et al.,* 2013[71]	NR	CDC Symptom inventory: NS
Peterson, *et al.,* 1990[70]	NR	NR
Strayer, *et al.,* 1994[72]	NR	Decreased used of medications for relief of CFS symptoms declined for rintatolimod but not compared with placebo

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
McKenzie, *et al.,* 1998[68]	1 rash with placebo	None	**Hydrocortisone vs. placebo** Suppression of adrenal glucocorticoid responsiveness: 12 vs. 0; p<0.001	**Hydrocortisone vs. placebo** *Events that differed* Increased appetite: 17 vs. 8; p=0.02 Weight gain: 19 vs. 8; p=0.006 Difficulty sleeping: 17 vs. 8; p=0.02	NR	Fair
Montoya, *et al.,* 2013[71]	0	1 patient with cancer in each group considered not related to intervention	0	0	Hoffman-La Roche; Stanford University	Fair
Peterson, *et al.,* 1990[70]	2 (1 in each group)	2 IgG and 3 placebo	**IgG vs. placebo** Headaches: 93% vs. 60%; p=0.03	20% overall	Baxter Healthcare Corp.	Fair
Strayer, *et al.,* 1994[72]	None	None	Insomnia more frequent among placebo, dry skin among rintatolimod	**Rintatolimod vs. placebo:** 706 vs. 711 events; p>0.90	Hemispherx Biopharma	Fair

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Strayer, *et al.,* 2012[73]	RCT of IV rintatolimod (Ampligen=antiviral and immunomodulatory drug) vs. placebo for underlying cause	**Rintatolimod vs. placebo** Mean age: 43 vs. 44 years % Female: 66 (no. NR) vs. 78 (no. NR) Race: NR	CDC (Holmes,1988) and (Fukuda, 1994) criteria **Inclusion:** Adults ≥18 years with diagnosis of CFS ≥ 12 months resulting in significant debilitation as measured by KPS, with ability to walk on the treadmill. Patients must have baseline laboratory documentation of euthyroid status, negative antinuclear antibody or negative anti-ed DNA, negative rheumatoid factor, and an erythrocyte sedimentation rate. **Exclusion:** Pregnant or lactating females, those who might become pregnant, chronic or intercurrent acute medical disorders, inability to return to investigators site for the study, prior participation in a study of Rintatolimond, medical need to continue taking aspirin or NSAIDs, treatment with glucocorticoids, mineralocorticoids, interferons, interleukin-2, systemic antivirals, gamma globulin or investigational drugs within the 8 weeks prior to study baseline.	**Rintatolimod vs. placebo** Mean: 9.6 vs. 9.7 years
Cognitive and behavior therapies				
Bazelmans, *et al.,* 2005[76]	Non-randomized study of group CBT vs. wait list for symptoms	**CBT vs. wait list** Mean age (SD): 37.4 (8.6) vs. 35.8 (9.0) years % Female: 68 (21/31) vs. 78 (28/36) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Fatigue score of ≥35 on the CIS scale, score of ≥700 on the SIP-8, and willing to stop other treatments for CFS during study. **Exclusion:** NR	**CBT vs. wait list** Mean (SD): 6.2 (5.2) vs. 5.3 (4.5) years

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Strayer, *et al.,* 2012[73]	Number approached: NR Number screened: NR Number eligible: 307 Number enrolled: 240 Number analyzed: 240	United States 12 centers	40 weeks	19% (46/240)	83% (194/234)
Cognitive and behavior therapies					
Bazelmans, *et al.,* 2005[76]	Number approached: NR Number screened: 139 Number eligible: NR Number enrolled: 67 (31 CBT, 36 wait list) Number analyzed: 65 (29 CBT, 36 wait list)	The Netherlands 2 University hospital clinics	6 months	**CBT vs. wait list:** 6% (2/31) vs. 0% (0/36)	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Strayer, *et al.,* 2012[73]	**Rintatolimod:** IV rintatolimod 400 mg twice weekly for 40 weeks **Placebo:** Placebo	**Rintatolimod vs. placebo** *Cardiopulmonary exercise tolerance (primary outcome)* Increase from baseline: 36.5% vs. 15.2%; p=0.047
Cognitive and behavior therapies		
Bazelmans, *et al.,* 2005[76]	**Group CBT:** 12 2-hour long group CBT sessions over 6 months aimed at challenging cognitions concerning a negative self-efficacy and somatic attributions; teaching patients to behave according to their own limits and to have adequate periods of rest and relaxation, therefore a graded activity program took place. **Wait list:** Wait list for duration of assessments.	**Group CBT vs. wait list** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* 6 months: 45.6 (9.6) vs. 48.4 (6.2); p=0.099

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Strayer, *et al.,* 2012[73]	NR	KPS score, ADLs, Vitality Score (SF-36), and General Health Perception (SF-36) measured pre and post, but not compared between rintatolimod and placebo groups
Cognitive and behavior therapies		
Bazelmans, *et al.,* 2005[76]	NR	**Group CBT vs. wait list** *Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)* 6 months: 1,736 (714) vs. 1,417 (444) Change from baseline: 29 vs. -293; p=0.004

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Strayer, *et al.,* 2012[73]	NR	**Rintatolimod vs. placebo** Decreased used of medications for relief of CFS symptoms: 68% vs. 55%; p=0.048
Cognitive and behavior therapies		
Bazelmans, *et al.,* 2005[76]	**Group CBT vs. wait list** *Mean (SD) hours worked per week* 6 months: 6.4 (11.7) vs. 6.7 (10.5); p=0.958	**Responders to CBT (n=10) vs. non-responders to CBT (n=17)** *Mean (SD) baseline differences* Hours worked per week: 10.9 (12.8) vs. 2.6 (6.6); p=0.062 Functional impairment SIP-8 scores: 1,330 (417) vs. 1,985 (730); p=0.031 Daily observed fatigue: 7.4 (2.6) vs. 9.7 (2.3); p=0.023 Daily observed pain: 4.5 (2.6) vs. 7.8 (3.5); p=0.026

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Strayer, *et al.,* 2012[73]	4 (2 in each group)	3 in each group with no differences between rintatolimod and placebo	Flu-like syndrome, chills, vasodilatation, and dyspnea were more frequent in rintatolimod vs. placebo (p<0.05)	99% rintatolimod and 97% placebo reported symptoms	Hemispherx Biopharma	Fair
Cognitive and behavior therapies						
Bazelmans, *et al.,* 2005[76]	NR	NR	NR	NR	National Foundation for Public Mental Health (Grant No. 4341)	Fair

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Burgess, *et al.,* 2012[77]	RCT of Face-to-face vs. telephone CBT for symptoms	**Face-to-face vs. telephone** Mean age (SD): 38.4 (9.7) vs. 36.7 (10.5) years % Female: 74 (26/35) vs. 82 (37/45) % White: 90 overall (NR per group) % With job to return to: 22 (7/35) vs. 45 (20/45)	CDC (Fukuda, 1994) and Oxford (Sharpe, 1991) criteria **Inclusion:** Ages 18-65 years, met both CDC and Oxford criteria, had CFS for <10 years, able to attend the hospital or have telephone sessions bi-weekly. **Exclusion:** Any medical condition that may have accounted for their fatigue, had started or changed medication within 3 months, were pregnant, had psychosis, drug abuse, a somatoform disorder or melancholic depression, a subtype of major depression with specific features including anhedonia, severe weight loss, psychomotor agitation or retardation, insomnia with early morning waking, and guilt.	**Face-to-face vs. telephone** Mean (SD): 4.20 (2.21) vs. 3.80 (2.09) years
Deale, *et al.,* 1997[78] Deale, *et al.,* 2001[79]	RCT of CBT vs. relaxation for symptoms	**CBT vs. relaxation** Mean age (SD): 31 (9) vs. 38 (11) years % Female: 70 (20/30) vs. 67 (20/30) Race: NR % Unemployed: 63 (19/30) vs. 77 (23/30) % On disability benefits: 53 (16/30) vs. 67 (20/30) % Current psychiatric diagnosis: 37 (11/30) vs. 40 (12/30) % Past psychiatric diagnosis: 30 (9/30) vs. 13 (4/30)	Oxford (Sharpe, 1991) and United States (Schluederberg, 1992) criteria **Inclusion:** Main complaint of medically unexplained, disabling fatigue of ≥6 months; with impairment of physical and mental activities; those taking antidepressants or anxiolytics (dose of ≤10 mg/day of diazepam or equivalent) were included if dose was stable for 3 months before study entry and during the trial. **Exclusion:** Somatization disorder, severe depression, ongoing physical investigations, concurrent new treatment, and inability to attend all treatment sessions.	**CBT vs. relaxation** Mean (SD): 3.4 (2.1) vs. 4.6 (3.3) years

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Burgess, *et al.,* 2012[77]	Number approached: NR Number screened: 410 Number eligible: 110 Number enrolled: 80 (35 face-to-face, 45 telephone) Number analyzed: 43 (23 face-to-face, 20 telephone)	United Kingdom CFS Research and Treatment Unit at the South London and Maudsley NHS Trust in London	12 months	**Face-to-face vs. telephone:** 34% (12/35) vs. 56% (25/45)	**Face-to-face vs. telephone:** 20% (7/35) vs. 33% (15/45) did not receive treatment Participants attended an average of 11.3 sessions
Deale, *et al.,* 1997[78] Deale, *et al.,* 2001[79]	Number approached: NR Number screened: 142 Number eligible: 67 Number enrolled: 60 (30 CBT, 30 relaxation) Number analyzed: 60 (30 CBT, 30 relaxation) in Deale, 1997; 53 (25 CBT, 28 relaxation) in Deale, 2001	United Kingdom Singe hospital clinic specializing in CFS	Deale, 1997: 6 months Deale, 2001: 5 years	**CBT vs. relaxation:** 10% (3/30) vs. 13% (4/30)	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Burgess, *et al.,* 2012[77]	**Face-to-face:** Up to 15 sessions of face-to-face CBT, first 2 sessions were 1.5 hours long with additional sessions lasting from 50-60 minutes. **Telephone:** Up to 14 sessions of CBT, first session was face-to-face and lasted up to 3 hours, with additional sessions conducted over the phone. *Note:* Both CBT interventions were aimed at helping patients to change behavioral and cognitive factors, focusing specifically on changing avoidance behavior, unhealthy sleep patterns, and unhelpful beliefs in order to improve levels of fatigue and disability. Individual sessions consisted of socialization with therapist and discussion of approach; agenda setting; homework reviewing; planning of future homework; discussion about how to manage sleep problems; ways to gradually increase activity without overdoing it; identifying and challenging unhelpful cognitions that were standing in the way of behavioral change; social factors if identified as important in perpetuating the symptoms and disability associated with their CFS; management of setbacks; and goals to work toward after treatment during followup.	**Face-to-face vs. telephone** *Mean (SD) Chalder fatigue scale scores (0-11 scale, lower scores indicate better health, score of ≥4 is cutoff for caseness); all p values are NS* 3 months: 7.08 (3.97) vs. 7.08 (3.56) 6 months: 5.75 (4.49) vs. 7.75 (3.77) 12 months: 6.83 (4.57) vs. 7.89 (3.75)
Deale, *et al.,* 1997[78] Deale, *et al.,* 2001[79]	**CBT:** 13 individual weekly or biweekly sessions over 4-6 months with the aim of showing patients that activity could be increased steadily and safely without exacerbating symptoms. **Relaxation:** 13 individual weekly or biweekly sessions over 4-6 months teaching progressive muscle relaxation, visualization, and rapid relaxation skills.	**CBT vs. relaxation** *Mean (SD) fatigue problem rating scores (0-8 scale, lower scores indicate better health)* 6 month followup: 3.4 (2.2) vs. 5.5 (1.9) p<0.001 for between group differences over time *Mean (SD) Chalder fatigue scale scores (0-11, scores of ≥4 indicate caseness or excessive fatigue, lower scores indicate better health)* 6 month followup: 4.1 (4.0) vs. 7.2 (4.0) p<0.001 for between group differences over time *% With fatigue rating by assessor at 3 months followup* Better or much better: 72 (18/25) vs. 17 (4/23); p<0.001 Unchanged or worse: 28 (7/25) vs. 83 (19/23) *% With score <4 on Chalder fatigue scale* 6 month followup: 63 (17/27) vs. 15 (4/26); p=0.001 5 year followup: 28 (7/25) vs. 25 (7/28); p=1.00

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Burgess, *et al.,* 2012[77]	NR	**Face-to-face vs. telephone** *Mean (SD) SF-36 physical functioning scale scores (0-100 scale, higher scores indicate better health)* 3 months: 58.97 (19.38) vs. 62.89 (20.33) 6 months: 65.78 (23.61) vs. 62.96 (20.36) 12 months: 62.32 (24.96) vs. 65.83 (21.73); p=0.043 for change from baseline for both groups
Deale, *et al.,* 1997[78] Deale, *et al.,* 2001[79]	NR	**CBT vs. relaxation** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* 6 month followup: 71.6 (28.0) vs. 38.4 (26.9); p<0.03 *% With good outcome on SF-36 physical functioning scale (increase of ≥ 50 from baseline to 6 months, or end score of ≥ 83):* 6 months followup: 63 (19/30) vs. 17 (5/30); difference of 46 (95% CI 24 to 68) p<0.001 5 year followup: 48 (12/25) vs. 32 (9/28); p=0.27 *% With rating by assessor at 3 month followup* Better or much better: 80 (20/25) vs. 26 (6/23); p<0.001 Unchanged or worse: 20 (5/25) vs. 74 (17/23)

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Burgess, *et al.,* 2012[77]	**Face-to-face vs. telephone** *Mean (SD) Work and social adjustment scale scores (0-45 scale, lower scores indicate better health)* 3 months: 23.35 (8.54) vs. 21.65 (7.42) 6 months: 19.40 (10.77) vs. 23.43 (8.06) 12 months: 20.83 (12.25) vs. 19.40 (8.73); p=0.013 for change from baseline for both groups	**Face to face vs. telephone** *Global improvement scores (% much better or very much better)* 6 months: 60 (15/25) vs. 40 (8/20) 12 months: 57 (13/23) vs. 55 (11/20)
Deale, *et al.,* 1997[78] Deale, *et al.,* 2001[79]	**CBT vs. relaxation** *Mean (SD) Work and social adjustment scale scores (0-8 scale, lower scores indicate better health)* 6 month followup: 3.3 (2.2) vs. 5.4 (1.8) p<0.001 for between group differences over time *% With full- or part-time employment at 5 year followup:* 56 (14/25) vs. 39 (11/28); p=0.28 *Mean (SD) hours worked per week (of employed persons, n=14 vs. 11) at 5 year followup:* 35.57 (8.11) vs. 24.00 (4.97); p<0.04	**CBT vs. relaxation** *% With global improvement rating* Better or much better at 6 month followup: 70 (19/27) vs. 31 (8/26); p<0.01 Unchanged or worse at 6 month followup: 30 (8/27) vs. 69 (18/26) Better or much better at 5 year followup: 68 (17/25) vs. 36 (10/28); p=0.05 *Other outcomes at 5 year follow* % With symptoms "steadily improved" not "consistently absent' or "mild": 68 (17/25) vs. 43 (12/28); p=0.05 % With complete recovery (no longer met CFS criteria, employed full-time, score <4 on Chalder fatigue scale, and score >83 on SF-36): 24 (6/25) vs. 4 (1/28); p=0.04 % No longer meeting U.K. criteria for CFS: 52 (13/25) vs. 39 (11/28); p=0.42 % With no relapses: 36 (9/25) vs. 7 (2/28); p=0.02 Mean (SD) number of relapses: 2.58 (2.21) vs. 4.08 (1.55); p<0.01

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Burgess, *et al.,* 2012[77]	NR	NR	NR	NR	NR	Fair
Deale, *et al.,* 1997[78] Deale, *et al.,* 2001[79]	NR	NR	NR	NR	South East Thames Regional Health Authority Locally Organized Research Scheme	Fair

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Goudsmit, *et al.,* 2009[80]	Non-randomized trial of counseling vs. wait list for symptoms	**Counseling vs. wait list** Mean age (SD): 39.6 (13.4) vs. 37.7 (14.4) years % Female: 73 (16/22) vs. 59 (13/22) % Employed full-time: 9 (2/22) vs. 0 (0/22) % On disability benefits: 14 (3/22) vs. 24 (5/22) % Changed job/reduced hours due to illness: 86 (18/21) vs. 95 (18/19) % On medication: 45.5 (10/22) vs. 54.5 (12/22)	Oxford (Sharpe, 1991) criteria **Inclusion:** NR **Exclusion:** NR	**Counseling vs. wait list** Mean (SD): 4.93 (3.6) vs. 2.92 (2.3) years; p<0.05
Jason, *et al.,* 2010[83]	RCT of buddy counseling vs. control for symptoms	**Buddy counseling vs. control** Mean age (SD): 56.8 (16.11) vs. 58.3 (9.35) years % Female: 87 (13/15) vs. 80 (12/15) % White: 80 (12/15) vs. 87 (13/15) % Other race: 20 (3/15) vs. 13 (2/15) % On disability: 47 (7/15) vs. 60 (9/15) % Unemployed: 33 (5/15) vs. 33 (5/15) % Working part- or full-time: 20 (3/15) vs. 7 (1/15)	CDC (Fukuda, 1994) criteria **Inclusion:** Diagnosed with CFS using Fukuda, 1994 criteria and felt they could benefit from intervention. **Exclusion:** NR	NR
Knoop, *et al.,* 2008[85] Tummers, *et al.,* 2010[92]	RCT of self-instruction therapy vs. wait list for symptoms	**Self-instruction vs. wait list** Mean age (SD): 37.6 (10.0) vs. 38.5 (10.6) years % Female: 82 (69/84) vs. 76 (65/85) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Age ≥18 years, spoke and read Dutch, not engaged in a legal procedure concerning disability-related financial benefits, scored ≥35 on the CIS fatigue severity subscale; total score of >700 on SIP-8. **Exclusion:** NR	**Self-instruction vs. wait list** Median (range): 72 (12-420) vs. 96 (12-420) months

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Goudsmit, *et al.,* 2009[80]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 44 (22 counseling, 22 wait list) Number analyzed: 44 (22 counseling, 22 wait list)	United Kingdom CFS specialist at Hospital	6 months	NR	NR
Jason, *et al.,* 2010[83]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 30 (15 buddy counseling, 15 control) Number analyzed: 30 (15 buddy counseling, 15 control)	United States, Chicago area Single site, Research Center at University	4 months	NR	NR
Knoop, *et al.,* 2008[85] Tummers, *et al.,* 2010[92]	Number approached: NR Number screened: NR Number eligible: 184 Number enrolled: 171 (85 self-instruction, 86 wait list) Number analyzed: 169 (84 self-instruction, 85 wait list)	The Netherlands Single tertiary care facility	6-12 months depending on length of treatment	**Stepped care program** **Self-instruction vs. wait list** Did not want to continue with CBT: 57% (48/84) vs. 22% (19/85)	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Goudsmit, *et al.,* 2009[80]	**Counseling:** Individual bi-monthly consultations consisting of diagnosis and information on CFS, daily diary competitions, advice about activity management, advice on limiting distress and increasing energy, and other advice dealing with diet, irritable bowel syndrome, and issues related to employment. **Wait list:** Wait list for duration of assessments.	**Counseling vs. wait list** *Mean (SD) Profile of fatigue-related symptoms scale scores (0-6 scale, lower scores indicate better health)* 6 months: 2.68 (1.41) vs. 3.84 (1.40); p=0.04
Jason, *et al.,* 2010[83]	**Buddy counseling:** 2-hours a week of student buddy support over 4 months consisting of emotional support, functional support (any direct help), and social support (such as working on household tasks during their visits). **Control:** No treatment for 4 months.	**Buddy counseling vs. control** *Mean (SD) FSS scores (9-63 scale, lower scores indicate better health)* 4 months: 52.9 (10.5) vs. 59.4 (3.7); p=0.04 *Mean (SD) SF-36 vitality scale scores (0-100 scale, higher scores indicate better health)* 4 months: 29.3 (13.9) vs. 24.7 (9.7); p<0.05
Knoop, *et al.,* 2008[85] Tummers, *et al.,* 2010[92]	**Self-instruction:** 16 weeks or more program of self-instruction booklet containing information about CFS and weekly assignments. **Wait list:** Wait list control for 6-12 months. ***Tummers, 2010*** **Stepped care:** Self-instruction as described above, then up to 14 sessions of individual CBT over 6 months **Care as usual:** Wait list as described above, then up to 14 sessions of individual CBT over 6 months	**Self-instruction vs. wait list** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Second assessment: 38.9 (12.1) vs. 46.4 (8.7); p<0.001 *% With reduction in CIS fatigue severity scores (CIS <35 and reliable change index of >1.96)* 27 (23/84; 95% CI 18 to 37) vs. 7 (6/85; 95% CI 2 to 13); OR 4.9 (95% CI 1.9 to 12.9); p<0.001 ***Tummers, 2010*** **Stepped care vs. care as usual** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Posttreatment: 35.1 (13.6) vs. 34.9 (13.8); difference 0.2 (95% CI -3.9 to 4.3); p=0.92 *% With reduction in CIS fatigue severity scores (CIS <35 and reliable change index of >1.96)* 49 (41/84) vs. 48 (41/85); OR 1.0 (95% CI 0.53 to 1.89); p=1.00

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Goudsmit, *et al.,* 2009[80]	NR	**Counseling vs. wait list** *Mean (SD) functional impairment scale scores (0-32 scale, lower scores indicate better health)* 6 months: 20.86 (6.09) vs. 22.73 (5.71); p=0.24
Jason, *et al.,* 2010[83]	NR	**Buddy counseling vs. control** *Mean (SD) SF-36 physical functioning scale scores (0-100 scale, higher scores indicate better health)* 4 months: 36.1 (14.1) vs. 36.0 (29.9); p=0.06
Knoop, *et al.,* 2008[85] Tummers, *et al.,* 2010[92]	NR	**Self-instruction vs. wait list** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Second assessment: 65.9 (23.2) vs. 60.2 (23.7); p=0.011 *Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)* Second assessment: 1,515 (545) vs. 1,319 (619); p<0.001 ***Tummers, 2010*** **Stepped care vs. care as usual** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Posttreatment: 71.6 (23.2) vs. 72.3 (24.3); difference -1.1 (95% CI -7.2 to 5.0); p=0.72 *Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)* Posttreatment: 826 (655) vs. 819 (653); difference 30.2 (95% CI -178 to 238); p=0.77

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Goudsmit, *et al.,* 2009[80]	NR	NR
Jason, *et al.,* 2010[83]	NR	NR
Knoop, *et al.,* 2008[85] Tummers, *et al.,* 2010[92]	NR	***Tummers, 2010*** **Stepped care vs. care as usual** Mean (SD) number of CBT sessions: 10.9 (4.4) vs. 14.5 (5.3); p<0.01 Median minutes in sessions (range): 420 (120-1,440 vs. 720 (120-2,040); p=0.01

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Goudsmit, *et al.,* 2009[80]	NR	NR	NR	NR	Action for ME	Poor
Jason, *et al.,* 2010[83]	NR	NR	NR	NR	National Institute of Allergy and Infectious Diseases (grant numbers AI36295 and AI49720)	Poor
Knoop, *et al.,* 2008[85] Tummers, *et al.,* 2010[92]	NR	NR	NR	NR	NR	Fair

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Lopez, *et al.,* 2011[86]	RCT of group CBT vs. control for symptoms	Mean age (SD): 45.9 (9.3) years % Female: 88 (61/69) % White: 77 (53/69) % Latino: 17 (12/69) % Caribbean Islander: 1 (7/69) % Biracial: 1 (7/69) % Another ethnic group: 3 (2/69) % Working full-time: 13 (9/69) % Working part-time: 19 (13/69) % Unemployed: 16 (11/69) % Retired: 4 (3/69) % Student: 3 (2/69) % On disability: 45 (31/69)	CDC (Fukuda, 1994) criteria **Inclusion:** 18-60 years, had ≥8th grade education, fluent in English. **Exclusion:** Active or previous medical condition that would explain the presence of chronic fatigue, positive for Lyme disease, had an infection that was treated with antibiotics within 3 weeks of the study, had surgery requiring general anesthesia within the past month of the study, were on any immunomodulator, had a history of major psychiatric illness, are currently in psychotherapy, had a history of substance or drug use within 2 years of the onset of CFS, or a history of major psychiatric illness.	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Lopez, *et al.,* 2011[86]	Number approached: NR Number screened: NR Number eligible: 113 Number enrolled: 69 (44 group CBT, 25 control) Number analyzed: 58 (38 group CBT, 20 control)	United States Single site, not described	12 weeks	**Overall:** 15.9% (11/69) **Group CBT vs. control:** 13.6% (6/44) vs. 20% (5/25)	NR, but group sessions, so except for the attrition, all assumed to adhere to program

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Lopez, *et al.,* 2011[86]	**Group CBT**: 12 weekly 2-hour group sessions of cognitive behavioral stress management consisting of 2 parts: 1) relaxation component and 2) didactic and discussion component; main technique used was cognitive restructuring targeting cognitive appraisals of ongoing stressors. **Control:** 1 session of psychoeducation summarizing strategies from the 12 week intervention.	**Group CBT vs. control** *Mean (SD) POMS-Fatigue subscale (0-28 scale, lower scores indicate better health)* After treatment: 17.85 (7.34) vs. 20.09 (6.99); p=0.06

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Lopez, *et al.,* 2011[86]	**Group CBT vs. control** *Mean (SD) QOLI scores* *Category score (range 1-4, lower scores indicate better health)* After treatment: 2.81 (1.15) vs. 3.26 (0.87); p=0.02 Raw score after treatment: 1.17 (1.83) vs. 0.82 (1.37); p=0.05 T score after treatment: 39.28 (14.17) vs. 36.42 (10.56); p=0.05	NR

Author, year	Employment outcomes	Other outcomes
Lopez, *et al.*, 2011[86]	NR	NR

Author, year	Withdrawals due to adverse event	Serious adverse events	other adverse events	Total adverse events	Sponsor	Quality rating
Lopez, *et al*., 2011 [86]	NR	NR	NR	NR	NIH	Poor

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
O'Dowd, *et al.*, 2006[88]	RCT of group CBT vs. group support vs. usual care for symptoms	**Group CBT vs. group support vs. usual care** Mean age (SD): 41.6 (12.0) vs. 38.8 (11.8) vs. 42.9 (11.6) years % Female: 54 (28/52) vs. 76 (38/50) vs. 71 (36/51) Race: NR % Discontinued main occupation due to CFS: 77 (36/52) vs. 63 (29/50) vs. 70 (35/51)	CDC (Fukuda, 1994) criteria **Inclusion:** Presentation consistent with ME/CFS described by Fukuda; able to read and understand patient information leaflet. **Exclusion:** Concurrent severe mental illness (i.e. psychosis and allied conditions); planned or concurrent rehabilitation; inability to attend all treatment sessions; or ongoing physical investigation.	**Group CBT vs. group support vs. usual care** % With symptoms for >60 months: 42 (21/50) vs. 50 (25/50) vs. 54 (27/50) % Diagnosed >12 months before study: 57% (28/49) vs. 45% (20/44) vs. 62% (29/47)

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
O'Dowd, *et al.,* 2006[88]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 153 (52 CBT, 50 support, 51 usual care) Number analyzed: 153 (52 CBT, 50 support, 51 usual care)	United Kingdom Pain Management Hospital	12 months	**Group CBT vs. group support vs. usual care:** 25% (13/52) vs. 8% (4/50) vs. 14% (7/51)	6% (3/52) of CBT group received support; 8% (4/50) of support group received CBT

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
O'Dowd, *et al.,* 2006[88]	**Group CBT:** 8 2-hour group CBT sessions bi-weekly aimed at modifying thoughts and beliefs about symptoms and illness; and modifying behavioral responses to symptoms and illness, such as rest, sleep, and activity; with goal to increase adaptive coping strategies and reduce the distress and disability of CFS. **Group Support:** 8 2-hour group education and support sessions bi-weekly focusing on sharing of experiences and learning of basic relaxation skills. **Usual care:** Managed in primary care and received no other intervention.	**Group CBT vs. group support vs. usual care** *Mean (SD) Chalder fatigue scale (0-33 scale, lower scores indicate better health)* 6 months: 17.9 (8.41) vs. 21.4 (7.55) vs. 21.8 (6.90); p=0.19 12 months: 17.4 (7.32) vs. 21.4 (7.79) vs. 18.8 (7.19); p=0.19 *Difference between groups from baseline at 12 months* CBT vs. support: -3.16 (95% CI -5.59 to -0.74); p=0.011 CBT vs. usual care: -2.61 (95% CI -4.92 to -0.30); p=0.027* Support vs. usual care: 0.55 (95% CI -1.56 to 2.66); p=NR *Note: this number is -2.16 in the text and -2.61 in the table

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
O'Dowd, *et al.*, 2006[88]	**Group CBT vs. group support vs. usual care** *Mean (SD) health related quality of life utility scores (higher scores indicate better health); all p values are NS* 6 months: 0.43 (0.28) vs. 0.34 (0.32) vs. 0.41 (0.25) 12 months: 0.45 (0.34) vs. 0.34 (0.35) vs. 0.46 (0.30) *Difference between groups from baseline at 12 months* CBT vs. support: 0.023 (95% CI -0.065 to 0.11) CBT vs. usual care: 0.029 (95% CI -0.052 to 0.11) Support vs. usual care: 0.006 (95% CI -0.082 to 0.095)	**Group CBT vs. group support vs. usual care** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health); all p values are NS* 6 months: 33.4 (9.04) vs. 32.3 (9.30) vs. 34.5 (9.95) 12 months: 35.2 (8.15) vs. 32.5 (7.91) vs. 35.0 (9.93) *% Reporting SF-36 score in normal range (score was on or above the 5th centile for the distribution, estimated as the mean -1.645 × SD for the gender-specific age group)* 6 months: 40 (17/43) vs. 24 (11/45) vs. 44 (20/46) 12 months: 46 (18/39) vs. 26 (12/46) vs. 44 (19/44); OR 1.03 (95% CI 0.38 to 2.73) for support vs. CBT; OR 1.51 (95% CI 0.58 to 3.91) for usual care vs. CBT; OR 1.47 (0.56 to 3.81) for support vs. usual care *% Reporting ≥15% increase from baseline* 6 months: 24 (11/43) vs. 33 (15/45) vs. 28 (13/46) 12 months: 26 (10/39) vs. 26 (12/46) vs. 43 (19/44) 6 and/or 12 months: 32 (15/NR) vs. 40 (19/NR) vs. 49 (23/NR); OR 1.29 (95% CI 0.58 to 2.86) for support vs. CBT; OR 1.68 (95% CI 0.76 to 3.69) for usual care vs. CBT; OR 1.30 (95% CI 0.61 to 2.76) *Mean incremental shuttle walking test; shuttles walked (number of complete 10m shuttles)* 6 months: 28.5 vs. 25.6 vs. 23.6 12 months: 28.9 vs. 24.1 vs. 24.2 *Difference between groups from baseline to 12 months* CBT vs. support: 1.16 (95% CI 0.94 to 1.43) CBT vs. usual care: 1.20 (95% CI 0.99 to 1.45) Support vs. usual care: 1.04 (95% CI 0.86 to 1.24) *Mean incremental shuttle walking test; normal walking speed (number of shuttles per level per minute)* 6 months:12.1 vs. 8.76 vs. 9.39 12 months: 12.2 vs. 10.0 vs. 9.46 6 and/or 12 months: 11.58 (0.71) vs. 9.82 (0.53) vs.8.76 (0.47); p=0.006 *Difference between groups from baseline to 12 months* CBT vs. support: 1.77 (95% CI 0.025 to 3.51); p=0.0055 CBT vs. usual care: 2.83 (95% CI 1.12 to 5.53); p=0.0055 Support vs. usual care: 1.06 (-0.37 to 2.49); p=0.15

Author, year	Employment outcomes	Other outcomes
O'Dowd, *et al.*, 2006[88]	NR	NR

Author, year	Withdrawals due to adverse event	Serious adverse events	other adverse events	Total adverse events	Sponsor	Quality rating
O'Dowd, *et al.*, 2006[88]	NR	NR	NR	NR	HTA Program (project NO. 974/41/08)	Fair

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Prins, *et al.,* 2001[89]	RCT of CBT vs. support vs. control for symptoms	**CBT vs. support vs. control** Mean age (SD): 36.2 (9.4) vs. 37.1 (10.6) vs. 36.7 (10.3) years % Female: 76 (70/92) vs. 79 (71/90) vs. 80.7 (71/88) Race: NR % Generally passive: 23 (21/92) vs. 19 (16/90) vs. 29 (24/88) % Moderately active: 62 (56/92) vs. 62 (53/90) vs/ 59 (50/88) % Generally active: 15 (13/92) vs./ 19 (16/90) vs. 12 (10/88)	CDC (Fukuda, 1994) criteria, except for the requirement of 4/8 additional symptoms to be present **Inclusion:** Ages 18-60 years and residence within 1.5 hours traveling time of 1 of the study centers. **Exclusion:** Previous or current participation in CFS research, pregnancy, and current treatment to achieve pregnancy.	**CBT vs. support vs. control** Mean (SD): 4.9 (4.8) vs. 6.6 (6.4) vs. 5.3 (5.4) years
Sharpe, *et al.,* 1996[90]	RCT of CBT vs. usual care for symptoms	**CBT vs. control** Mean age (SD): 34 (9.1) vs. 38 (11.8) years % Female: 60 (18/30) vs. 77 (23/30) Race: NR % Not working or studying: 87 (26/30) vs. 50 (15/30) % Major depressive disorder: 20 (6/30) vs. 20 (6/30) % Any depressive disorder: 53 (16/30) vs. 57 (17/30) % Any anxiety disorder: 47 (14/30) vs. 50 (15/30) % Any anxiety or depression disorder: 67 (20/30) vs. 67 (20/30) % Somatization disorder: 10 (3/30) vs. 10 (3/30)	Oxford (Sharpe 1991) criteria **Inclusion:** Ages 18-60 years, with major complaint of fatigue. **Exclusion:** Currently receiving psychotherapy or antidepressant drugs; unwilling to accept randomization or unavailable for followup; met criteria for severe depression or had history of bipolar disorder, schizophrenia, or substance misuse; or at significant risk of suicide or in need of urgent psychiatric treatment.	**CBT vs. control** Mean (SD): 33.6 (9.1) vs. 29.7 (24.1) months

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Prins, *et al.,* 2001[89]	Number approached: NR Number screened: 476 Number eligible: 377 Number enrolled: 278 (93 CBT, 94 support, 91 control) Number analyzed: 196 (58 CBT, 80 support, 78 control)	The Netherlands 3 centers	14 months	**Overall:** 33.1% (92/278) **CBT vs. support vs. control:** 40.8% (38/93) vs. 35.1% (33/94) vs. 23.1% (21/91)	NR
Sharpe, *et al.,* 1996[90]	Number approached: NR Number screened: 123 Number eligible: 62 Number enrolled: 60 (30 CBT, 30 control) Number analyzed: 60 (30 CBT, 30 control)	United Kingdom, Oxford 2 Centers	12 months	Only 1/60 did not complete 12 month followup data	All CBT patients completed their intervention

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Prins, *et al.,* 2001[89]	**CBT:** 16 1-hour sessions of individual CBT over 8 months consisting of: explanation of the model of perpetuating factors; challenging of fatigue-related cognitions; encouragement to attain and maintain a base level of physical activity; development of a structured activity program; planned outline of work rehabilitation; and relapse prevention. **Support:** 11 1.5-hour support group meetings over 8 months with the goal of offering mutual understanding and recognition by means of exchanging experiences with one central theme during each meeting. **Control:** No interventions offered.	**CBT vs. support vs. control** *% With improvement on CIS (reliable change of >1.64 and score ≤36)* 8 months: 33 (27/83) vs. 13 (10/80) vs. 13 (10/78); p=0.003 (CBT vs. support) and p=0.005 (CBT vs. control) 14 months: 35 (20/58) vs. 13 (8/62) vs. 17 (13/76); p=0.009 (CBT vs. support) and p=0.026 (CBT vs. control) **Treatment effects CBT vs. support on CIS** 8 months: 6.0 (95% CI 3.1 to 9.0); p=0.0001 14 months: 5.8 (95% CI 2.2 to 9.4); p=0.0015 **Treatment effects CBT vs. control on CIS** 8 months: 6.0 (95% CI 3.1 to 9.0); p=0.0001 14 months: 5.6 (95% CI 2.1 to 9.0); p=0.0016
Sharpe, *et al.,* 1996[90]	**CBT:** 16 1-hour sessions of individual CBT over 4 months emphasizing cognitive techniques and tailored for patients with CFS, strategies to reduce excessive perfectionism and self criticism, and an active problem solving approach to interpersonal and occupational difficulties was also employed. **Control:** Patients were followed by their General Practitioner in their usual way.	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Prins, *et al.,* 2001[89]	**Treatment effects CBT vs. support on EuroQol scale** 8 months: -7.8 (95% CI -14.0 to -1.8); p=0.0114 14 months: -9.2 (95% CI -15.6 to -2.8); p=0.0049 **Treatment effects CBT vs. control on EuroQol scale** 8 months: -4.0 (95% CI -10.0 to 2.0); p=0.1878 14 months: -2.3 (95% CI -8.4 to 3.8); p=0.4619	**CBT vs. support vs. control** *% With improvement on KPS (improvement from baseline of ≥10 points and final score ≥80)* 8 months: 41 (29/71) vs. 16 (11/69) vs. 12 (9/75); p=0.001 (CBT vs. support) and p<0.0001 (CBT vs. control) 14 months: 49 (28/57) vs. 19 (12/62) vs. 23 (17/75); p=0.001 (CBT vs. support and CBT vs. control) **Treatment effects CBT vs. support on KPS** 8 months: -5.7 (95% CI -8.4 to -3.1); p=0.0001 14 months: -6.3 (95% CI -9.6 to -3.0); p=0.0002 **Treatment effects CBT vs. control on KPS** 8 months: -5.2 (95% CI -7.8 to -2.6); p=0.0001 14 months: -5.4 (95% CI -8.6 to -2.2); p=0.0009 **Treatment effects CBT vs. support on SIP-8** 8 months: 217 (95% CI 26 to 408); p=0.0261 14 months: 263 (95% CI 38 to 488); p=0.0223 **Treatment effects CBT vs. control on SIP-8** 8 months: 213 (95% CI 22 to 403); p=0.0287 14 months: 222 (95% CI 3 to 441); p=0.0470
Sharpe, *et al.,* 1996[90]	NR	**CBT vs. control** *Achieved KPS score of ≥80* 5 months: 27% (8/30) vs. 20% (6/30); difference of 7 (95% CI -15 to 28) 8 months: 53% (16/30) vs. 30% (9/30); difference of 23 (95% CI 0 to 48) 12 months: 73% (22/30) vs. 27% (8/30); difference of 47 (95% CI 24 to 69) *Improvement of ≥10 points on KPS* 5 months: 23% (7/30) vs. 7% (2/30); difference of 17 (95% CI 0 to 34) 8 months: 60% (18/30) vs. 20% (6/30); difference of 40 (95% CI 17 to 63) 12 months: 73% (22/30) vs. 23% (7/30); difference of 50 (95% CI 28 to 72)

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Prins, *et al.,* 2001[89]	**Treatment effects CBT vs. support on hours worked on 24-hour timetable** 8 months: -5.6 (95% CI -11.7 to 0.4); p=0.0681 14 months: -9.6 (95% CI -17.1 to -2.0); p=0.0132 **Treatment effects CBT vs. control on hours worked on 24-hour timetable** 8 months: -2.9 (-8.8 to 3.0); p=0.3362 14 months: -5.9 (95% CI -13.2 to 1.4); p=0.1134	**CBT vs. support vs. control** *% With self-rated improvement (patient indicating they were fully recovered or felt much better)* 8 months: 57 (42/74) vs. 17 (12/71) vs. 30 (23/78); p<0.0001 (CBT vs. support) and p=0.001 (CBT vs. control) 14 months: 50 (29/58) vs. 15 (9/62) vs. 32 (24/76); p<0.001 (CBT vs. support) and p=0.034 (CBT vs. control)
Sharpe, *et al.,* 1996[90]	NR	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Prins, *et al.,* 2001[89]	NR	NR	NR	NR	Health Insurance Council	Fair
Sharpe, *et al.,* 1996[90]	NR	NR	NR	NR	Welcome Trust	Good

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Taylor, 2004[91]	RCT of counseling vs. wait list for symptoms	**Counseling vs. wait list** Mean age (SD): 49.0 (10.9) vs. 44.9 (9.7) years % Female: 91 (21/23) vs. 100 (24/24) % Minority: 17 (4/23) vs. 17 (4/24) % Working full-time: 9 (2/23) vs. 21 (5/24) % Working part-time: 22 (5/23) vs. 8 (2/24) % Unemployed: 70 (16/23) vs. 71 (17/24)	CDC (Fukuda, 1994) **Inclusion:** Adults with CFS by Fukuda criteria. **Exclusion:** Psychiatric illness that would rule out CFS diagnosis, untreated hypertension.	NR
Tummers, *et al.,* 2012[93]	RCT of self-instruction therapy vs. wait list for symptoms	**Self-instruction vs. wait list** Mean age (SD): 36.3 (12.1) vs. 36.4 (13.6) years % Female: 74 (46/62) vs. 82 (50/61) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Age 18-65 years, were severely fatigued (≥35 on the fatigue severity subscale of the CIS), were fatigued for ≥6 months, were severely disabled (≤70 on physical and/or social functioning subscale of SF-36), reported ≥4 of 8 additional symptoms: unrefreshing sleep, post exertional malaise, headache, muscle pain, multi-joint pain, sore throat, tender lymph nodes, impairment of concentration or memory. **Exclusion:** Those with the presence of somatic diseases or psychiatric disorders and the use of medication that could explain the fatigue.	**Self-instruction vs. wait list** Median (range): 48 (6-464) vs. 60 (6-625) months

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Taylor, 2004[91]	Number approached: NR Number screened: 52 Number eligible: 50 Number enrolled: 47 (23 counseling, 24 wait list) Number analyzed: 47 (23 counseling, 24 wait list)	United States, Chicago area Single site, not described	12 months	None dropped out	Stated program adherence was good, but otherwise NR
Tummers, *et al.,* 2012[93]	Number approached: NR Number screened: 181 Number eligible: 142 Number enrolled: 123 (62 self-instruction, 61 wait list) Number analyzed: 111 (55 self-instruction, 56 wait list)	The Netherlands Single tertiary care facility	6 months	**Self-instruction vs. wait list** 11% (7/62) vs. 8% (5/61)	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Taylor, 2004[91]	**Counseling:** 8 sessions of a group illness-management program occurring biweekly over 4 months consisting of check-ins, reporting of self-monitored goal attainment, educational lecture and discussion of self-selected, CFS-relevant topics including activity pacing using the Envelope Theory, cognitive coping skills training, relaxation and meditation training, employment issues and economic self-sufficiency, personal relationships, traditional and complementary medical approaches, and nutritional approaches. This was followed by a 1 month break and then 7 months of 1-on-1 peer counseling, which consisted of self-advocacy training, continued monitoring of goal attainment, and ongoing case coordination services. **Wait list:** On waiting list for 12 months, then given program as described above. Results of this group after they received the program are NR.	NR
Tummers, *et al.,* 2012[93]	**Self-instruction:** Up to 20 weeks of guided self-instruction which included setting goals reviewing of precipitating and perpetuating factors, challenging of fatigue-related cognitions, reducing focus on fatigue, physical activity level adapted for either relatively-active person or a low-active person, gradually asked to increase activity, challenging of beliefs that activity would exacerbate symptoms, begin plan for resuming work, modifying excessive expectations regarding the response of their social environment to their symptoms, gradually increase mental and social activities, and relapse prevention. **Wait list:** Waitlist control for duration of intervention.	**Self-instruction vs. wait list** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Second assessment: 39.6 (14.1) vs. 48.3 (8.1); p<0.01 *% With reduction in CIS fatigue severity scores (CIS <35 and reliable change index of >1.96)* 33 (18/55) vs. 9 (5/56); OR 5.0 (95% CI 1.69 to 14.57) ***Subanalysis of baseline group with SF-36 physical functioning score ≤70*** **Self-instruction (n=53) vs. wait list (n=50)** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Second assessment: 38.9 (14.3) vs. 50.1 (6.2) Change from baseline: -12.4 vs. -2.4; difference: -9.9 (95% CI, -5.4 to -14.3); p<0.01

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Taylor, 2004[91]	**Counseling vs. wait list** *Mean (SD) QLI scores (0-30 scale, higher scores indicate better outcomes)* Overall at 4 months: 13.2 (3.8) vs. 14.6 (4.8) Overall at 12 months: 15.7 (3.7) vs. 14.6 (4.1) Change in score at 12 months from baseline: 2.6 vs. 0.6; p<0.05 Health and function subscale at 4 months: 12.8 (1.8) vs. 13.6 (2.1) Health and function subscale at 12 months: 14.1 (1.7) vs. 13.6 (1.8) Social and economic subscale at 4 months: 15.2 (0.8) vs. 15.5 (1.0) Social and economic subscale at 12 months: 15.6 (0.8) vs. 15.5 (0.9) Psychological and spiritual subscale at 4 months: 15.0 (1.1) vs. 15.2 (1.3) Psychological and spiritual subscale at 12 months: 15.5 (1.1) vs. 15.1 (1.2) Family subscale at 4 months: 15.4 (1.0) Family subscale at 12 months: 15.6 (0.8) vs. 15.5 (0.9) Change in score at 12 months from baseline: 0.2 vs. -0.2; p<0.05	NR
Tummers, *et al.*, 2012[93]	NR	**Self-instruction vs. wait list** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Second assessment: 65.4 (24.9) vs. 59.3 (22.9); p=0.08 ***Subanalysis of baseline group with SF-36 physical functioning score ≤70*** **Self-instruction (n=53) vs. wait list (n=50)** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Second assessment: 63.0 (25.9) vs. 53.4 (18.7) Change from baseline: 18.5 vs. 9.6, difference: 9.05 (95% CI, 0.2 to 17.9); p<0.05

Author, year	Employment outcomes	Other outcomes
Taylor, 2004[91]	NR	NR
Tummers, *et al.,* 2012[93]	NR	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Taylor, 2004[91]	None withdrew	NR	NR	NR	U.S. Department of Education National Institute on Disability and Rehabilitation Research Grant #H133G000097	Good
Tummers, *et al.,* 2012[93]	NR	NR	NR	NR	Dutch Medical Research Council ZonMW	Good

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Tummers, *et al.,* 2013[94] Secondary analysis of Knoop, *et al.,* 2008[85] & Tummers, *et al.,* 2012[93] combined	RCT of self-instruction therapy vs. wait list for symptoms	**Self-instruction vs. wait list** Mean age (SD): 37.2 (10.9) vs. 37.9 (12.1) years % Female: NR Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Patients included in Knoop, 2008 and Tummers, 2012 RCTs. **Exclusion:** Those who did not have complete data at the second assessment.	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Tummers, *et al.,* 2013[94] Secondary analysis of Knoop, *et al.,* 2008[85] & Tummers, *et al.,* 2012[93] combined	See Knoop, 2008 and Tummers, 2012	The Netherlands Single tertiary care facility	6-12 months based on the RCTs	NR	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Tummers, *et al.*, 2013[94] Secondary analysis of Knoop, *et al.*, 2008[85] & Tummers, *et al.*, 2012[93] combined	**Self-instruction:** As described in Knoop, 2008 and Tummers, 2012. **Wait list:** As described in Knoop, 2008 and Tummers, 2012.	**Interaction tests for potential moderators from linear regression models (95% CI)** Age (years): 0.15 (0.01 to 0.045); p<0.05 Depression: 0.15 (0.04 to 1.95); p=0.04 *Perpetuating factors* Self-efficacy: -0.06 (-1.18 to 0.56); p=0.48 Somatic attribution: 0.10 (-0.32 to 1.43); p=0.21 Avoidance of activity: 0.17 (0.03 to 1.78); p=0.04 Focus on bodily symptoms: -0.02 (-0.61 to 0.52); p=0.88 **Interaction tests for potential moderators from logistic regression models (95% CI)** Age (years): 1.06 (0.99 to 1.13); p=0.10 Depression: 1.40 (1.08 to 1.82); p=0.01 *Perpetuating factors* Self-efficacy: 0.81 (0.62 to 1.05); p=0.11 Somatic attribution: 1.13 (0.87 to 1.46); p=0.36 Avoidance of activity: 1.34 (1.03 to 1.74); p=0.03 Focus on bodily symptoms: 1.02 (0.87 to 1.20); p=0.80

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Tummers, *et al.*, 2013[94] Secondary analysis of Knoop, *et al.*, 2008[85] & Tummers, *et al.*, 2012[93] combined	NR	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Tummers, *et al.*, 2013[94] Secondary analysis of Knoop, *et al.*, 2008[85] & Tummers, *et al.*, 2012[93] combined	NR	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	other adverse events	Total adverse	Sponsor	Quality rating
Tummers, *et al.*, 2013[94] Secondary analysis of Knoop, *et al.*, 2008[85] & Tummers, *et al.*, 2012[93] combined	NR	NR	NR	NR	See Knoop, 2008 and Tummers, 2012	See Knoop, 2008 and Tummers, 2012

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Wearden, *et al.,* 2010[95] ***FINE Trial*** Wearden, *et al.,* 2012[96] Wearden and Emsley, 2013[97]	RCT of pragmatic rehab vs. supportive listening vs. usual care for symptoms	**Pragmatic rehab vs. supportive listening vs. usual care** Mean age: 43.74 vs. 45.13 vs. 44.92 years % Female: 78 (74/95) vs. 79 (80/101) vs. 76 vs. 76/100) Race: NR % Ambulatory: 90 (85/95) vs. 87 (88/101) vs. 88 (88/100) % Met London ME criteria: 30 (28/95) vs. 31 (31/101) vs. 33 (33/100) % Any anxiety diagnosis: 27 (21/95) vs. 20 (17/101) vs. 26 (22/100) % Any depression diagnosis: 19 (18/95) vs. 15 (15/101) vs. 20 (20/100) % With ≥2 comorbidities: 34 (32/95) vs. 32.7 (33/101) vs. 43 (43/100) % With 1 comorbidity: 22 (21/95) vs. 28 (29/101) vs. 24 (24/100) % With no comorbidities: 44 (42/95) vs. 39 (39/101) vs. 33 (33/100)	Oxford (Sharpe ,1991) criteria **Inclusion:** Ages ≥18 years, scored ≤70% on SF-36 physical functioning scale, scored ≥4 on Chalder fatigue scale. **Exclusion:** Fit criteria for antisocial, borderline, or paranoid personality disorders; active suicidal ideation; unable to read or write English; currently under taking systemic psychological therapies for CFS/ME; had received pragmatic rehabilitation in the past year.	Median (range): 7 (0.5-51.7) years

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Wearden, *et al.,* 2010[95] ***FINE Trial*** Wearden, *et al.,* 2012[96] Wearden and Emsley, 2013[97]	Number approached: 449 Number screened: 338 Number eligible: NR Number enrolled: 296 (95 pragmatic rehab, 101 supportive listening, 100 usual care) Number analyzed: 257 (81 pragmatic rehab, 90 supportive listening, 86 usual care)	United Kingdom 186 general practitioners referred patients	18 weeks treatment; 70 weeks total followup	**Overall:** 13.2% (39/296) **Pragmatic rehab vs. supportive listening vs. usual care:** 14.7% (14/95) vs. 10.9% (11/101) vs. 14.0% (14/100) 1 in supportive listening group subsequently received diagnosis of multiple sclerosis (misdiagnosis)	**Pragmatic rehab:** 3/95 didn't receive intervention **Supportive listening:** 10/101 didn't receive intervention 1/101 received pragmatic rehab instead

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Wearden, *et al.,* 2010[95] ***FINE Trial*** Wearden, *et al.,* 2012[96] Wearden and Emsley, 2013[97]	**Pragmatic rehab:** 10 sessions over an 18-week period of a program of graded return to activity; designed collaboratively by the patient and therapist, which encourages patients to regularize their sleep patterns and includes relaxation exercises to address somatic symptoms of anxiety. An additional component to address concentration and memory problems was also included. **Supportive listening:** 10 sessions over an 18-week period of listening therapy based on non-directive counseling, with therapist aiming to provide an empathic and validating environment in which the patient can discuss his or her concerns and work towards resolution of whichever problems the patient wishes to prioritize. **Usual care:** Practitioners managed their patients as they saw fit, but were not referred for systematic psychological therapies for CFS/ME during the 18-week treatment period.	**Pragmatic rehab vs. supportive listening vs. usual care** *Mean (SD) Chalder fatigue scale scores (items scored dichotomously; lower scores indicate better outcomes)* 20 weeks: 8.39 (3.67) vs. 9.67 (2.76) vs. 9.32 (3.18); treatment effect estimate -1.18, 95% CI -2.18 to -0.18; p=0.021 for pragmatic rehab vs. usual care 70 weeks: 8.72 (3.65) vs. 9.39 (3.21) vs. 9.48 (2.71); p=NS **Pragmatic rehab vs. usual care** *Mean (SD) Chalder fatigue scale scores (items scored 0-3 and summed to total of 0-33; lower scores indicate better outcomes)* 20 weeks: 22.78 (8.56) vs. 26.27 (7.68) 70 weeks: 23.90 (8.34) vs. 26.02 (7.11) **Significant regression coefficients for interaction between putative moderators and treatment (pragmatic rehab vs. usual care)** HADS baseline depression score: -0.67 (95% CI -1.25 to -0.10); p=0.022 HADS baseline total score: -0.30 (95% CI -0.58 to -0.02); p=0.039 EQ-5D self-care scale, those with severe problems: -28.72 (95% CI -32.14 to -25.31); p<0.001 **Significant regression coefficients to predict change in Chalder fatigue scale scores (pragmatic rehab vs. usual care)** Age: -0.10 (95% CI -0.19 to -0.003); p=0.044 Duration of illness: -0.01 (95% CI -0.02 to -0.003); p=0.008 EQ-5D mobility scale; those with severe problems: -2.95 (95% CI -5.51 to -0.40); p=0.024

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Wearden, *et al.,* 2010[95] ***FINE Trial*** Wearden, *et al.,* 2012[96] Wearden and Emsley, 2013[97]	NR	**Pragmatic rehab vs. supportive listening vs. usual care** *Mean percentage scores (SD) on SF-36 physical functioning scale (0-100 scale, higher scores indicate better outcomes)* 20 weeks: 39.94 (25.21) vs. 33.28 (22.94) vs. 40.27 (26.45); treatment effect estimate -7.54, 95% CI -2.96 to -0.11; p=0.035 for supportive listening vs. usual care 70 weeks: 43.27 (27.38) vs. 35.72 (25.94) vs. 39.83 (27.77); p=NS

Author, year	Employment outcomes	Other outcomes
Wearden, *et al.*, 2010[95] *FINE Trial* Wearden, *et al.*, 2012[96] Wearden and Emsley, 2013[97]	NR	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Wearden, *et al.,* 2010[95] ***FINE Trial*** Wearden, *et al.,* 2012[96] Wearden and Emsley, 2013[97]	Unclear, 1 each in pragmatic rehab and supportive listening withdrew due to nurse therapist safety concern, not otherwise described	None reported	See Total adverse events	Overall: 4 (herpes simplex infection, attempted suicide, bleeding peptic ulcer, and recurrence of cancer; all deemed unrelated to interventions)	United Kingdom Medical Research Council (G200212) and the United Kingdom Department of Health; and the University of Manchester	Good

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Complementary and alternative medicine				
Hobday, *et al.,* 2008[99]	RCT of low sugar, low yeast vs. healthy eating for symptoms	**Low sugar/low yeast vs. healthy eating** Mean age (SD): 44 (10.2) vs. 42 (11.9) years % Female: 88 (22/25) vs. 78 (21/27) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Diagnosis of CFS, no other criteria described. **Exclusion:** Pregnant women; those taking oral contraceptives, hormone therapy, steroids, NSAID, or immunosuppressants; already following significant dietary changes; taking vitamin and mineral supplements above recommended dose; or diagnosed with an eating disorder.	NR
Öckerman, 2000[100]	Crossover RCT of antioxidant of pollen (Polbax) vs. placebo for underlying cause	Mean age: 50 years % Female: 86 (19/22) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18-70 years, symptom score ≥49 for 13 symptoms and ≥5 for total wellbeing. **Exclusion:** Active smokers, dental treatment, electrical hypersensitivity, pollen allergy, use of drugs and other medial diseases and/or treatment.	NR
The, *et al.,* 2007[101]	RCT of acclydine (IGF1 stimulant) vs. placebo for underlying cause	**Acclydine vs. placebo** Mean age (SD): 40.9 (9.4) vs. 43.4 (11.2) years % Female: 77 (no. NR) vs. 59 (no. NR) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18-65 years, IGFBP3/IGF1 ratio >2.5 **Exclusion:** Psychiatric comorbidities, pregnant or lactating women, lactose intolerance, or taking psychotropic drugs or experimental medications. Note: Healthy controls were included to compare hormone blood levels, outcome NR here	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Complementary and alternative medicine					
Hobday, *et al.,* 2008[99]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 52 Number analyzed: 39	United Kingdom, London CFS clinic	24 weeks	**Overall:** 25% (13/52) **Low sugar/low yeast vs. healthy eating:** 24% (6/25) vs. 26% (7/27)	**Low sugar/low yeast vs. healthy eating:** 24% vs. 67%
Öckerman, 2000[100]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 22 Number analyzed: 22 (5 placebo-pollen, 5 pollen-placebo, 6 placebo-placebo, 6 pollen-pollen)	NR	3 months	**Overall:** 4.5% (1/22)	NR
The, *et al.,* 2007[101]	Number approached: NR Number screened: 112 Number eligible: 88 Number enrolled: 57 Number analyzed: 57	The Netherlands University medical center	14 weeks	**Overall:** 3.5% (2/57) **Acclydine vs. placebo:** 3.3% (1/30) vs. 3.7% (1/27)	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Complementary and alternative medicine		
Hobday, *et al.,* 2008[99]	**Low sugar/low yeast:** Adapted from Beat Candida Cook Book (White, 1999) - omission of all sugar containing foods, refined carbohydrates, and yeast containing foods, alcohol, caffeine; limited fruit, milk; encouraged to have one live yogurt per day. **Healthy eating:** High fiber, 5 servings of fruit and vegetables per day, reduced fat and refined carbohydrate, fish 2 times a week.	**Low sugar/low yeast vs. healthy eating** *Mean (SD) Chalder Fatigue Scale scores (scores of ≥4 indicate caseness for fatigue, lower score indicates better health)* 24 weeks: 16.0 (8.2) vs. 17.7 (10.0); p=0.6 *Mean (SD) SF-36 vitality subscale scores (0-100 scale, higher score indicates better health)* 24 weeks: 29.8 vs. 36.2; p=0.39
Öckerman, 2000[100]	**Pollen:** Antioxidant extract of pollen (Polbax) **Placebo**: Placebo *Note:* All patients given pollen or placebo for 3 months followed by a 2-week wash-out period with no treatment followed by 3-month of pollen or placebo. Groups equal pollen (given pollen in both 3 month periods), placebo-placebo (given placebo in both 3 month periods), pollen-placebo (given pollen in first 3 month period, then placebo in second 3 month period), and placebo-pollen (given placebo in first 3 month period, then pollen in second 3 month period)	**Pollen vs. placebo** *Mean fatigue score (Likert scale 0=no problem to 10=extremely serious symptom)* 3 months: 7.52 vs. 7.14; p=NR Change from baseline: -0.43 vs. -0.18; p<0.05
The, *et al.,* 2007[101]	**Acclydine:** Acclydine (increases IGF1 levels) with amino acid supplement **Placebo:** Placebo with amino acid supplement	**Acclydine vs. placebo** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* 14 weeks: 42.4 (11.6) vs. 43.0 (12.6); p=0.70

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Complementary and alternative medicine		
Hobday, *et al.,* 2008[99]	NR	**Low sugar/low yeast vs. healthy eating** *Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, higher score indicates better health)* 24 weeks: 42.3 (29.2) vs. 52.2 (24.1); p=0.25
Öckerman, 2000[100]	**Pollen vs. placebo** *Mean total well-being score (0-10 Likert type scale, lower scores indicate better health; Likert scale 0=no problem to 10=extremely serious symptom)* 3 months: 7.14 vs. 6.66; p=NR Change from baseline: -1.66 vs. -0.21; p<0.01 *Change in total well-being after treatment*; p value NR Worse: 9.5% (2/21) vs. 18% (4/22) No change: 29% (6/21) vs. 59% (13/22) Better: 62% (13/21) vs. 23% (5/22)	NR
The, *et al.,* 2007[101]	NR	**Acclydine vs. placebo** *Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)* 14 weeks: 1,228.1 (619.7) vs. 1,120.2 (543.0); p=0.65

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Complementary and alternative medicine		
Hobday, *et al.,* 2008[99]	NR	NR
Öckerman, 2000[100]	NR	NR
The, *et al.,* 2007[101]	NR	**Acclydine vs. placebo** *Mean (SD) physical activity level over a 12-day period (measured by actometer attached to the ankle)* 14 weeks: 64.9 (23.4) vs. 64.9 (23.5); p=0.42

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Complementary and alternative medicine						
Hobday, *et al.,* 2008[99]	NR	NR	NR	NR	NR	Fair
Öckerman, 2000[100]	NR	None	Gastro intestinal - 1 or 2 patients	NR	NR	Poor
The, *et al.,* 2007[101]	NR	None	NR	NR	Optipharma	Good

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Vermeulen and Scholte, 2004[102]	Open-label RCT of acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination for underlying cause	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination** Mean age (SD): 37(11) vs. 38 (11) vs. 42 (12) years % Female: 77 (23/30) vs. 77 (23/30) vs. 77 (23/30) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Meet CDC criteria for CFS, no other criteria described. **Exclusion:** Patients with an underlying organic cause, substance misuse, and severe psychiatric disorder.	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination** Median (range): 5.5 (1.0-23.0) vs. 3.0 (0.5-25.0) vs. 6.0 (1.0-21.0) years
Walach, *et al.,* 2008[103]	RCT of distant healing vs. usua care (waiting) for symptoms	**Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care** Mean age (SD): 47.5 (10.7) vs. 48.1 (10.0) vs. 46.2 (10.9) vs.50.4 (12.8) years % Female: 74.3 vs. 76.5 vs. 76.6 vs. 75.0 Mean length of unemployment (SD): 36.3 (38.2) vs. 34.8(49.6) vs. 27.7 (22.3) vs.28.7 (27.4) months Race: NR	CDC (Fukuda, 1994) or Oxford (Sharpe, 1991)criteria **Inclusion:** Patients 18 years or older who met the Fukuda or Oxford Criteria. **Exclusion:** Patients with other chronic conditions of co-morbidities that typically rule out a diagnosis of CFS (cancer, hepatitis, or depression, pregnancy, patents with a serious acute illness or hospital admission in the 3 months prior to entry.	**Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care** Mean (SD): 11.3 (9.4) vs. 9.6 (6.7) vs. 9.6 (8.6) vs. 11.9 (9.9) years

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Vermeulen and Scholte, 2004[102]	Number approached: NR Number screened: 114 Number eligible: 114 Number enrolled: 90 Number analyzed: 89	The Netherlands CFS clinic	24 weeks	**Overall:** 20% (18/90) **Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination:** 27% (8/30) vs. 13% (4/30) vs.20% (6/30)	NR
Walach, *et al.,* 2008[103]	Number approached: NR Number screened: 1,400 Number eligible: 875 Number enrolled: 411 Number analyzed: 409	Germany and Austria Private practices for environmental medicine specializing in CFS	6 months treatment Followup to 18 months	**Overall:** 3.2% (13/411) **Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care**: 1.9% (2/105) vs. 5.8% (6/102) vs. 2.1% (2/94) vs. 2.8% (3/108)	Healer non-adherence to protocol and replaced: 7.4% (34/462) Healer withdrew practice: 6.7% (31/462)

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Vermeulen and Scholte, 2004[102]	**Acetyl-L-carnitine:** Acetyl-L-carnitine 2g/day **Propionyl-L-carnitine:** Propionyl-L-carnitine 2 g/day **Combination:** Acetyl-L-carnitine 2g/day + propionyl-L-carnitine 2 g/day	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination** *Mean (SD) MFI-20 scores (4-20 scale, lower scores indicate better health)* General fatigue at 16 weeks: 16.5 (4.1) vs. 15.7 (4.0) vs. 16.9 (3.2) General fatigue at 24 weeks: 15.9 (4.2) vs. 16.5 (3.1) vs. 17.3 (3.3); p=0.004 for propionyl-L-carnitine change from baseline; p=0.000 for combo change from baseline Physical fatigue at 16 weeks: 15.8 (4.4) vs. 15.8 (4.0) vs. 16.1 (3.5) Physical fatigue at 24 weeks: 15.7 (4.4) vs. 16.4 (3.2) vs. 16.5 (3.4) Mental fatigue at 16 weeks: 15.0 (2.9) vs. 13.8 (4.1) vs. 14.2 (4.0) Mental fatigue at 24 weeks: 15.1 (3.6) vs. 13.9 (3.5) vs. 14.6 (4.0); p=0.015 for acetyl-L-carnitine change from baseline
Walach, *et al.,* 2008[103]	**Distant healing:** Received distant healing from 3 healers who were allowed to use whichever techniques they used in their normal practice; techniques included either prayer or imagining the transmission of 'healing energy, 'light', or 'healing power' **Usual care:** Deferred treatment for duration of treatment *Note: Patients were also randomized to being blinded or unblinded to treatment allocation*	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Vermeulen and Scholte, 2004[102]	NR	NR
Walach, *et al.*, 2008[103]	NR	**Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care** *Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, lower score indicates better health)* 6 months: 34.69 (9.77) vs. 34.79 (10.41) vs. 35.08 (10.01) vs. 33.46 (9.68); p=NS Change from baseline: 3.66 (6.83) vs. 3.04 (7.38) vs. 3.29 (7.28) vs. 0.75 (7.85); p=NS Covariance analysis effect for blinded vs. unblinded treatment: -1.54 (SE 0.70) 95% CI -2.91 to -0.18

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Vermeulen and Scholte, 2004[102]	NR	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination** *% Improved on CGI* 24 weeks: 59 (17/29) vs. 63 (16/unclear) vs. 37 (11/30)
Walach, *et al.,* 2008[103]	NR	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Vermeulen and Scholte, 2004[102]	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination:** 10% (3/29) vs. 7% (2/30) vs. 10% (3/30)	NR	Overstimulated feeling and sleeplessness	NR	Unclear	Fair
Walach, *et al.,* 2008[103]	NR	NR	NR	NR	NR	Good

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Weatherley-Jones, *et al.,* 2004[104]	RCT of homeopathy vs. placebo for symptoms	**Homeopathy vs. placebo** Mean age (SD): 38.9 (10.8) vs. 38.8 (11.3) years % Female: 57 (no. NR) vs. 62 (no. NR) Race: NR	Oxford (Sharpe, 1991) criteria **Inclusion:** Patients over 18 years of age, meeting the Oxford criteria. **Exclusion:** Patients with primary major depression, bipolar disorders, psychosis, eating disorders, substance abuse/dependence, and somatization disorders.	**Homeopathy vs. placebo** Mean (SD): 4.8 (4.3) vs. 3.7 (2.4) years
Williams, *et al.,* 2002[105]	Crossover RCT of melatonin vs. phototherapy for symptoms	Overall, for those completing study Mean age (SD): 44.5 (11.1) years % Female: 57 (17/30) Race: NR	Oxford (Sharpe, 1991) Criteria **Inclusion:** Patients diagnosis with CFS by the Oxford criteria. **Exclusion:** Various reasons including diagnostic uncertainty and reluctance to meet the practical demands of the protocol.	Mean (SD): 3.6 (3.3) years

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Weatherley-Jones, *et al.,* 2004[104]	Number approached: NR Number screened: 214 Number eligible:168 Number enrolled: 103 Number analyzed: 86	United Kingdom 1 specialty clinic in CFS and 1 in infectious disease	6 months	**Overall:** 11% (11/103) **Homeopathy vs. placebo:** 10% (5/50) vs. 11% (6/53)	NR
Williams, *et al.,* 2002[105]	Number approached: NR Number screened: 62 Number eligible: 52 Number enrolled: 42 Number analyzed: 30	United Kingdom University hospital	12 weeks treatment, 12 week washout, then 12 week crossover and 12 week washout	**Overall:** 29% (12/42) **Melatonin vs. phototherapy:** 27% (6/22) vs. 30% (6/20)	Random pill counts showed no major shortfalls

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Weatherley-Jones, *et al.,* 2004[104]	**Homeopathy:** Homeopathic prescriptions given after consultations, single remedies prescribed at each consultation, and occasionally >1 remedy; remedies changed throughout, but must be only those remedies which have been proved **Placebo:** Placebo prescribed in the same manner as homeopathy	**Homeopathy vs. placebo** *Mean change from baseline (SD) MFI-20 scores (4-20 scale, lower score indicates better health)* General fatigue: 2.70 (3.93) vs. placebo 1.35 (2.66), p=0.04 Physical fatigue: 2.13 (4.00) vs. 1.28 (2.74); p=0.21 Mental fatigue: 2.70 (4.01) vs. 2.05 (2.86); p=0.30 *Mean change from baseline (SD) FIS (0-40 scale for each subscale, except 0-80 scale for social subscale, lower score indicates better health)* Cognitive dimension: 4.88 (9.3) vs. 4.21 (7.18); p=0.61 Physical dimension: 4.98 (8.5) vs. 5.30 (6.69); p=0.98 Social dimension: 7.92 (18.02) vs. 8.20 (14.06); p=0.79
Williams, *et al.,* 2002[105]	**Melatonin:** Oral melatonin 5 mg daily **Phototherapy:** Phototherapy with 2500 Lux lightbox 30 minutes in morning	**Melatonin vs. phototherapy** *Median (IQR) visual analog scale score for How fatigued are you? (1-10 scale, lower score indicates better health)* After treatment: 6.1 (4.8 to 8.0) vs. 6.6 (5.0 to 8.0); p=NS *Median (IQR) Mental Fatigue Inventory scores (0-36 scale, lower score indicates better health)* After treatment: 23 (15.0 to 27.0) vs. 24 (21.0 to 29.0); p=NS *Median (IQR) SF-36 vitality subscale scores (0-100 scale, lower score indicates better health)* After treatment: 20 (10.0 to 40.0) vs. 20 (10.0 to 25.0); p=NS

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Weatherley-Jones, *et al.,* 2004[104]	NR	**Homeopathy vs. placebo** *Mean change from baseline (SD) Functional Limitations Profile scores (scale unclear, higher score indicates better health)* Physical dimension: 5.11 (8.82) vs. 2.72 (8.40), p=0.04 Psychosocial dimension: 9.81 (14.19) vs. 6.76 (10.67); p=0.14
Williams, *et al.,* 2002[105]	NR	**Melatonin vs. phototherapy** *Median (IQR) SF-36 physical functioning subscale scores (0-100 scale, lower score indicates better health)* After treatment: 42.5 (16.3 to 53.8) vs. 45 (22.5 to 60.0); p=NS

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Weatherley-Jones, *et al.,* 2004[104]	NR	NR
Williams, *et al.,* 2002[105]	NR	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Weatherley-Jones, *et al.,* 2004[104]	NR	NR	NR	NR	NR	Fair
Williams, *et al.,* 2002[105]	NR	NR	NR	NR	NR	Fair

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Exercise				
Fulcher and White, 1997[106]	RCT (with control treatment crossover after the first followup examination) of graded aerobic exercise vs. flexibility exercises and relaxation therapy for symptoms	Mean age (SD): 37.2 (10.7) years % Female: 74 (49/66) Race: NR	Oxford (Sharpe, 1991) criteria **Inclusion:** Patients meeting the Oxford criteria. **Exclusions:** Patients excluded for psychiatric disorders, not including simple phobias, using the clinical interview for the DSM-III-R or for co-morbid symptomatic insomnia.	Median (range): 2.7 years (0.6-19.0)
Ho, *et al.,* 2012[107]	RCT of qigong exercise vs. no qigong exercise for symptoms	**Exercise vs. control** Mean age: 42.1 vs. 42.7 years % Female: 76% (25/33) vs. 84% (26/31) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Adults ages 18-55 years who were available at all testing points, and met Fukuda criteria. **Exclusion:** Those diagnosed with medical conditions that might explain the presence of chronic fatigue. Examples of these diagnoses include cancer, hypothyroidism, sleep apnea, narcolepsy, hepatitis B or C virus infection, substance abuse, mental disorders and severe obesity. Persons who had participated in qigong training within the previous 6 months and those with serious medical conditions that might limit participation were also excluded.	≥6 months

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Exercise					
Fulcher and White, 1997[106]	Number approached: NR Number screened: 167 Number eligible: 66 Number enrolled: 66 Number analyzed: 59 (29 exercise, 30 control)	United Kingdom, London Department of Psychological Medicine, St Bartholomew's and the Royal London Medical School	12 weeks, 1 year followup	**Overall:** 79% (7/59) **Exercise vs. control:** 13% (4/29) vs. 10% (3/30)	NR
Ho, *et al.,* 2012[107]	Number approached: NR Number screened: 1,441 Number eligible: 236 Number enrolled: 70 Number analyzed: 52 (27 exercise, 25 control)	Hong Kong Special Administrative Region of China	4 months (5 weeks training in qigong exercise and 12 weeks of followup)	**Overall:** 26% (18/70) **Exercise vs. control:** 18% (27/35) vs. 19% (25/35)	No followup after 5 weeks: 8.6% (3/35, controls)

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Exercise		
Fulcher and White, 1997[106]	**Exercise:** Exercise treatment, weekly for 12 weeks of supervised treatment. **Control:** 12 weeks of flexibility and relaxation sessions.	**Exercise vs. control** *Mean (SD) Chalder fatigue scale score (0-56 scale, lower scores indicate better health)* 12 weeks: 20.5 (8.9) vs. 27.4 (7.4); p=0.004 *Mean (SD) Visual analog scale total fatigue score (unclear scale, 200 noted as 'normal', lower scores indicate better health)* 12 weeks: 253 (48) vs. 286 (67); p=0.04 *Mean (SD) Visual analog scale physical fatigue score (unclear scale, 100 noted as 'normal', lower scores indicate better health)* 12 weeks: 130 (28) vs. 154 (34); p=0.006 *Mean (SD) Visual analog scale mental fatigue score (unclear scale, 100 noted as 'normal', lower scores indicate better health)* 12 weeks: 124 (31) vs. 132 (39); p=0.38
Ho, *et al.,* 2012[107]	**Exercise:** Qigong exercise 30 minutes every day, at home. **Control:** Refrained from qigong exercise.	**Exercise vs. control** *Mean (SD) Chalder fatigue scale total fatigue scores (0-56 scale, lower score indicates better health)* 4 months: 21.6 (10.4) vs. 32.1 (8.8) p=0.000, between groups over time *Mean (SD) Chalder fatigue scale physical fatigue scores (0-32 scale, lower score indicates better health)* 4 months: 12.9 (6.1) vs. 20.3 (5.7) p=0.000, between groups over time *Mean (SD) Chalder fatigue scale mental fatigue scores 0-24 scale, lower score indicates better health)* 4 months : 8.8 (4.6) vs. 11.9 (3.8) p=0.012 , between groups over time

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Exercise		
Fulcher and White, 1997[106]	NR	**Exercise vs. control** *Mean (SD) SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health)* 12 weeks: 69 (18.5) vs 55 (21.8); p=0.01
Ho, *et al.,* 2012[107]	NR	**Exercise vs. control** *Mean (SD) QOL SF-12 mental functioning score (6 items scored from 0 to 100, higher scores indicate better health)* 4 months: 42.7 (7.2) vs. 35.7 (9.5); p=0.001 *Mean (SD) QOL SF-12 physical functioning score (6 items scored from 0 to 100, higher scores indicate better health)* 4 months: 40.1 (6.9) vs. 37.8 (5.6); p=0.484

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Exercise		
Fulcher and White, 1997[106]	**Exercise vs. all participants** (due to control allowed to crossover to exercise) Working full- or part-time at 1 year followup: 66% (31/47) vs. 39% (26/66); 95% CI 9% to 44%; p=NR	**Exercise vs. control** *Self-rated CGI score after 12 weeks* % Very much better: 31 (9/29) vs. 7 (2/30) % Much better: 24 (7/29) vs. 20 (6/30) % A little better: 38 (11/29) vs. 60 (18/30) % No change: 3 (1/29) vs. 10 (3/30) % A little worse: 3 (1/29) vs.0 (0/30) % Much worse: 0 (0/29) vs. 3 (1/30) % Very much worse: 0 (0/29) vs. 0 (0/30) p=0.05 for between groups comparison *Median (IQR) peak O_2 consumption (ml/kg/minute)* After 12 weeks: 35.8 (30.8-40.7) vs. 29.8 (24.7 (34.9); p=0.03 Median increase in peak O2 consumption: 13% vs. 6% Median increase in isometric strength: 26% vs. 15%; p=0.20 *Rated self as better at 1 year followup:* 74% (35/47)
Ho, *et al.,* 2012[107]	NR	**Exercise vs. control** *Mean (SD) telomerase activity (arbitrary unit)* 4 months: 0.178 (0.201) vs. 0.104 (0.059) p=0.029, between groups over time

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Exercise						
Fulcher and White, 1997[106]	NR/unclear ("minimal adverse effects" but no number reported)	NR	NR	NR	Linbury Trust, a Sainsbury charitable trust	Fair
Ho, *et al.,* 2012[107]	NR	NR	NR	None	Centre on Behavioral Health Research Fund, University of Hong Kong	Fair

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Moss-Morris, *et al.,* 2005[108]	RCT of graded exercise vs. standard medical care for symptoms	**Exercise vs. control** Mean age (SD): 36.7 (11.8) vs. 45.5 (10.4) years % Female: 60 (15/25) vs. 79 (19/24) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18-65 years and meeting Fukuda criteria. **Exclusion:** Patients unable to exercise for medical reasons or patients already performing regular exercise.	Median (range): 3.08 years (0.5-45 years)
Sutcliffe, *et al.,* 2010[109]	RCT of orthostatic training vs. placebo for symptoms	**Orthostatic training vs. control** Mean age: 48 vs. 48 years % Female: 79 (15/19) vs. 84 (16/19) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Ages ≥18 years with diagnosis of CFS under Fukuda criteria. **Exclusion:** Use of drugs which can affect the autonomic nervous system that cannot be safely discontinued, inability to stand up for 40 minutes, or pregnancy.	NR
Combination therapies				
Jason, *et al.,* 2007[84] Jason, *et al.,* 2009[82] Hlavaty, *et al.,* 2011[81]	RCT of CBT vs. COG vs. ACT vs. relaxation for symptoms	Mean age: 43.8 years % Female: 83 (no. NR) % White: 88 (no. NR) % Black: 4 (no. NR) % Latino: 4 (no. NR) % Asian-American: 4 (no. NR) % On disability: 25 (no. NR) % Unemployed: 24 (no. NR) % Working part-time: 20 (no. NR) % Working full-time: 19 (no. NR) % Retired: 6 (no. NR) % Part-time student: 4 (no. NR) % Full-time student: 1 (no. NR) % Working part-time and on disability: 2 (no. NR) % Lifetime axis I diagnosis: 62 (no. NR) % Current axis I diagnosis: 39 (no. NR)	CFS Questionnaire, psychiatric assessment for DSM-IV diagnosis, and medical assessment **Inclusion:** Ages ≥18 years, not pregnant, able to read and speak English, considered to be physically capable of attending the scheduled sessions. **Exclusion:** Persons who used wheelchairs and who were bedridden or housebound; lifelong fatigue; >4 secondary symptoms of CFS; BMI >45 kg/m^2; melancholic depression or bipolar depression; alcohol or substance abuse disorder; autoimmune thyroiditis; cancer; lupus; or rheumatoid arthritis.	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Moss-Morris, *et al.,* 2005[108]	Number approached: NR Number screened: 51 Number eligible: 49 Number enrolled: 49 Number analyzed: 49 (25 exercise, 24 control)	Auckland, New Zealand CFS private general practice centers	12 weeks, 6 month followup	**Overall:** 12% (6/49) **Exercise vs. control:** 12% (3/25) vs. 13% (3/24)	**Overall:** 88% (43/49) **Exercise vs. control:** 88% (22/25) vs. 88% (21/24)
Sutcliffe, *et al.,* 2010[109]	Number approached: 59 Number screened: 52 Number eligible: 49 Number enrolled: 38 Number analyzed: 36 (18 orthostatic training, 18 control)	Newcastle, United Kingdom UK NIHR Biomedical Research Centre in Ageing, Royal Victoria Infirmary, Newcastle University	6 months	**Overall:** 26% (10/38) **Orthostatic training vs. control:** NR	**Overall completion of fatigue questionnaires:** 24 **Orthostatic training vs. control:** 12 vs. 12
Combination therapies					
Jason, *et al.,* 2007[84] Jason, *et al.,* 2009[82] Hlavaty, *et al.,* 2011[81]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 114 (29 CBT, 28 COG, 29 ACT, 28 Relaxation) Number analyzed: 114 (29 CBT , 28 COG, 29 ACT, 28 Relaxation) in Jason, 2007; 81 (49 staying within their energy envelope, 32 going beyond their energy envelope) in Jason, 2009; 82 (22 CBT, 22 COG, 18 ACT, 20 Relaxation) in Hlavaty, 2011	United States, Chicago area Single site, not described	12 months	Average drop out rate: 25%, but NR per group	Participants attended an average of 10 out of 13 sessions (range: 1-13) Hlavaty, 2011 focuses on subgroup analysis based on homework compliance, groups defined by amount of homework completed as follows: Minimum (0-25% completed) vs. moderate (25.1%-75% completed) vs. maximum (75.1%-100% completed)

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Moss-Morris, *et al.,* 2005[108]	**Exercise:** Graded exercise therapy, 30 minutes per day 5 days per week. **Control:** Standard medical care.	**Exercise vs. control** *Mean (SD) Chalder fatigue scale total fatigue scores (0-56 scale, lower scores indicate better health)* 12 weeks: 13.91 (10.88) vs. 24.41(9.69); p=0.02 *Mean (SD) Chalder fatigue scale physical fatigue subscale scores (0-32 scale, lower score indicates better health)* 12 weeks: 7.91 (7.06) vs. 14.27 (5.75); p=0.02 *Mean (SD) Chalder fatigue scale mental fatigue subscale scores (0-24 scale, lower score indicates better health)* 12 weeks: 6.00 (4.06) vs. 10.14 (4.27); p=0.03
Sutcliffe, *et al.,* 2010[109]	**Orthostatic training**: Standing with upper back against a wall, heels 15 cm from the wall with a cushioned 'drop zone', maintained position without movement for 40 minutes or until symptoms of CFS occur. **Control:** Standing against a wall as described above for only 10 minutes, also taught to perform gentle flexion and extension exercises with their calf muscles while standing against the wall, to enhance believability, counter venous pooling and prevent any possible orthostatic training effect.	**Orthostatic training vs. control** Improvement of ≥10 points on FIS at 6 months: 50% (7/14) vs. 38% (5/13); p=NR
Combination therapies		
Jason, *et al.,* 2007[84] Jason, *et al.,* 2009[82] Hlavaty, *et al.,* 2011[81]	**CBT:** 13 sessions of individual CBT, held once every 2 weeks, with graded activity developed in collaboration with the participant; beginning modestly, with activity and rest pre-planned and time-contingent rather than symptom-driven; negative automatic thoughts were reviewed and cognitive strategies were introduced to develop new ways of thinking. **Cognitive therapy (COG):** 13 sessions, held once every 2 weeks, of broad-based cognitive approach focused on developing cognitive strategies to better tolerate and reduce stress and symptoms, and to lessen self-criticism. **Anaerobic activity therapy (ACT):** 13 sessions, held once every 2 weeks, of anaerobic activity therapy focused on developing individualized, constructive and pleasurable activities with reinforcement. **Relaxation:** 13 sessions, held once every 2 weeks, focusing on progressive muscle relaxation techniques, breathing, yoga form stretching, and thematic imagery relaxation; participants were shown how to use relaxation techniques in stressful situations.	**CBT vs. COG vs. ACT vs. Relaxation** *Mean (SD) FSS scores (9-63 scale, lower score indicates better health)* 12 months: 5.37 (1.19) vs. 5.87 (1.01) vs. 5.77 (1.43) vs. 5.62 (1.06); p=NR ***Jason, 2009 data: comparison by energy envelope (data estimated from figure)*** **Stayed within envelope vs. outside envelope** 6 months: 5.7 vs. 6.1; p=NR 12 months: 5.3 vs. 6.3 Change at 12 months from baseline: -0.9 vs. 0.1; p<0.01 ***Hlavaty, 2011 data: comparison by homework compliance level*** **Minimum vs. moderate vs. maximum** Change in score at 12 months from baseline: -0.17 (0.73) vs. -0.51 (1.00) vs. -0.54 (1.09); p=NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Moss-Morris, *et al.,* 2005[108]	NR	**Exercise vs. control** *Mean (SD) SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health)* 12 weeks: 69.05 (21.94) vs. 55.00 (22.94); p=0.49
Sutcliffe, *et al.,* 2010[109]	NR	**Orthostatic training vs. control** Difference in mean (SD) blood pressure drop with active stand at 6 months: 6 mmHg; 95% CI, 0.0 to 12.6; p=0.05
Combination therapies		
Jason, *et al.,* 2007[84] Jason, *et al.,* 2009[82] Hlavaty, *et al.,* 2011[81]	**CBT vs. COG vs. ACT vs. Relaxation** *Mean (SD) QLS scores (16-112 scale, higher score indicates better health)* 12 months: 69.10 (18.99) vs. 72.52 (10.84) vs. 63.00 (13.86) vs. 72.00 (19.70); p=NR	**CBT vs. COG vs. ACT vs. Relaxation** *Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, higher score indicates better health)* 12 months: 58.64 (30.44) vs. 61.09 (23.74) vs. 39.72 (27.63) vs. 61.20 (27.70) p<0.01 for CBT and COG over time vs. ACT over time % Achieving clinically significant improvement: 18.2 vs. 30.4 vs. 11.1 vs. 21.7; p=NS ***Jason, 2009 data: comparison by energy envelope (data estimated from figure)*** **Stayed within envelope vs. outside envelope** 6 months: 58 vs. 48;p=NR 12 months: 65 vs. 43 Change at 12 months from baseline: 17 vs. 0; p=0.03 ***Hlavaty, 2011 data: comparison by homework compliance level*** **Minimum vs. moderate vs. maximum** Change in score at 12 months from baseline: 6.99 (19.30) vs. 7.55 (18.85) vs. 17.50 (18.09); p=NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Moss-Morris, *et al.,* 2005[108]	NR	**Exercise vs. control** *Self-rated CGI at 6 months* % Much or very much improved: 54 (12/22) vs. 24 (5/21); p=0.04
Sutcliffe, *et al.,* 2010[109]	NR	NR
Combination therapies		
Jason, *et al.,* 2007[84] Jason, *et al.,* 2009[82] Hlavaty, *et al.,* 2011[81]	**CBT vs. COG vs. ACT vs. Relaxation** % Employed at 12 month followup: 62 vs. 56 vs. 33 vs. 43; p=NS	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Moss-Morris, *et al.,* 2005[108]	1 patient withdrew due to injured calf	NR	10 of 25 patients refused to repeat fitness test as felt initial test harmful	2% (1/49)	University of Auckland Staff Grants	Fair
Sutcliffe, *et al.,* 2010[109]	NR	NR	NR	NR	Northern Regional CFS/ME Clinical Network	Fair
Combination therapies						
Jason, *et al.,* 2007[84] Jason, *et al.,* 2009[82] Hlavaty, *et al.,* 2011[81]	NR	NR	NR	NR	NIAID (Grant No. AI 49720)	Fair

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Núñez, *et al.*, 2011[87]	RCT of CBT + GET vs. usual care for symptoms	**CBT + GET vs. usual care** Mean age: 42.7 vs. 44.3 years % Female: 93 (53/58) vs. 86 (48/57) Race: NR % Actively working: 16 (9/58) vs. 20 (11/57) % Unemployed: 9 (5/58) vs. 4 (2/57) % Temporary work disability: 31 (18/58) vs. 23 (13/57) % Permanent work disability: 33 (19/58) vs. 45 (25/57) % Retired: 0 (0/58) vs. 2 (1/57) % Other: 11 vs. 7 Mean number of co-morbidities: 1.60 vs. 1.46 % Fibromyalgia: 75 (43/58) vs. 63 (37/57) % Sicca syndrome: 9 (5/58) vs. 20 (11/57) % Dysthymia: 35 (20/58) vs. 23 (13/57) % Thyroid disturbances: 12 (7/58) vs. 16 (9/57) % Dysmenorrhea/endometriosis: 0 vs. 0 % Chemical sensitivity: 5 (3/58) vs. 7 (4/57) % Other co-morbidities: 23 (13/58) vs. 18 (10/57) Mean HADS-anxiety score: 11 vs. 11 Mean HADS-depression score: 12 vs 11	CDC (Fukuda, 1994) criteria **Inclusion:** Diagnosed with CFS using Fukuda, 1994 criteria. **Exclusion:** Past or current diagnosis of a major depressive disorder with psychotic or melancholic features according to Fukuda criteria; physical diseases that could cause fatigue, including morbid obesity, hypothyroidism, Cushing syndrome, anemia (blood hemoglobin <10 g/L), diabetes, active neoplastic or infectious disease, inflammatory rheumatic disease, and patients unable to participate fully in study procedures; involved in ongoing legal or occupational conflicts.	**CBT + GET vs. usual care** Mean: 32 vs. 33 months

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Núñez, *et al.*, 2011[87]	Number approached: NR Number screened: 276 Number eligible: 134 Number enrolled: 120 (60 each group) Number analyzed: 115 (58 CBT + GET vs. 57 usual care)	Spain 1 University hospital clinic	2.5-3 months of treatment, 12 months followup after treatment	**Overall:** 4.2% (5/120) **CBT vs. usual care** 3.3% (2/60) vs. 5.0% (3/60)	NR, but group sessions, so except for the attrition, all assumed to adhere to program

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Núñez, *et al.,* 2011[87]	**CBT + GET:** Group CBT, 9 twice weekly 90-minute sessions during 2.5-3 months; content included: psychoeducational interventions to explain the multi-factorial character of CFS, progressive muscle relaxation procedures, sleep hygiene patterns, detection and control of verbal and non-verbal pain-inducing attitudes, cognitive thought patterns, information about the relationship between vegetative and anxiety symptoms, modification of type A behavioral patterns, improvement in assertiveness, patterns to increase attention and memory, sensorial focalization for sexual inhibition, and disease relapse prevention. Group GET, 3 times a week 1-hour sessions, over intermittent periods of 10 minutes for 3 months, with gradual increases in aerobic exercise at a rate of 5 minutes per session and complementary activities such as flexibility exercise and relaxation therapy were included. Total exercise load was maintained or increased to a maximum of 40 minutes per day according to tolerance. **Usual care:** Usual CFS therapy including exercise counseling and conventional pharmacological symptomatic treatment. *Note:* Symptomatic pharmacological treatment was the same in both groups: paracetamol 1-3 g/day and ibuprofen 600-1,800 mg/day if reported inflammation and zolpidem 10 mg/night if reported insomnia.	**CBT + GET vs. usual care** *Mean FIS (0-160 scale, higher score indicates better health)* 12 months: 139.2 vs. 137.4; p=NS

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Núñez, *et al.*, 2011[87]	NR	**CBT + GET vs. usual care** *Mean SF-36 physical function subscale (0-100 scale, higher score indicates better health)* 12 months: 32.63 vs. 38.28; p=NS

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
Núñez, *et al.*, 2011[87]	NR	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Núñez, *et al.*, 2011[87]	NR	NR	NR	NR	Generalitat of Catalonia, SGR 2009-1158 and CIBEROBN, Carlos III Health Institute, Majadahonda, Madrid	Fair

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Wearden, *et al.,* 1998[75]	RCT of GET + fluoxetine vs. GET alone vs. fluoxetine alone vs. control for symptoms	**Overall, GET + fluoxetine vs. GET vs. fluoxetine vs. control** Mean age: 38.7, 38.2 vs. 40.4 vs. 38.8 vs. 37.6 years % Female: 71 (97/136), 67 (22/33) vs. 79 (27/34) vs. 77 (27/35) vs. 62 (21/34) Race: NR	Oxford (Sharpe, 1991) criteria **Inclusion:** Ages ≥ 18 years, meeting Oxford criteria, principle complaint of fatigue, impairment in 3 out of 4 areas of activity. **Exclusion** Medical cause of fatigue.	≥ 6 months

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Wearden, *et al.,* 1998[75]	Number approached: NR Number screened: 227 Number eligible: 165 Number enrolled: 136 Number analyzed: ITT: 136 (33 GET + fluoxetine, 34 fluoxetine, 35 GET, 34 control) Completed trial: 96 (19 GET + fluoxetine, 23 fluoxetine, 25 GET, 29 control)	Northwest England and North Wales University department of medicine out-patient clinic	26 weeks	**Overall:** 29% (40/136) **GET + fluoxetine vs. fluoxetine vs. GET vs. control** 42% (14/33) vs. 32% (11/34) vs. 29% (10/35) vs. 17% (5/29)	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
Wearden, *et al.,* 1998[75]	**GET + fluoxetine**: Preferred aerobic activity (usually walking/jogging, swimming, or cycling) performed for 20 minutes, ≥3/week, with low initial intensity that was gradually increased based on hear rate plus fluoxetine 20 mg daily. **Fluoxetine**: Fluoxetine 20 mg daily plus placebo exercise program of being told to keep doing what they were doing and no other advice. **GET:** Preferred aerobic activity (usually walking/jogging, swimming, or cycling) performed for 20 minutes, ≥3/week, with low initial intensity that was gradually increased based on hear rate plus placebo drug. **Control:** Placebo drug plus placebo exercise program of being told to keep doing what they were doing and no other advice.	**GET + fluoxetine vs. GET vs. fluoxetine vs. control** *Mean (95% CI) Chalder fatigue scale scores (unclear scale, lower scores indicate better health)* 0-12 weeks: -5.7 (-9.2 to -2.2) vs. -2.1 (-4.9 to 0.6) vs. -1.6 (-4.4 to 1.2) vs. -2.0 (-4.1 to 0.1) 26 weeks: -6.0 (-9.7 to -2.3) vs. -5.7 (-9.5 to -1.9) vs. -3 (-5.9 to -0.2) vs. -2.7 (-5.4 to 0.01) *% non-cases of fatigue (Chalder fatigue scale score <4)* 12 weeks: 18 (6/33) vs. 3 (1/34) vs. 1 (3/35) vs. 6 (2/34) 26 weeks: 18 (6/33) vs. 18 (6/34) vs. 6 (2/ 35) vs. 6 (2/34) p=0.025 for exercise interventions combined vs. others *Exercise improved fatigue scale scores* 0-12 weeks: mean change=2.l (95% CI -0.6 to 4.8), p=0.13 26 weeks: mean change=2.9 (95% CI -0.2 to 6.1), p=0.07

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
Wearden, *et al.*, 1998[75]	NR	**GET + fluoxetine vs. GET vs. fluoxetine vs. control** *Mean (SD) functional work capacity (amount of O2 consumed in the final minute of exercise per kg of body weight)* Mean change (95% CI) functional work capacity (amount of O2 consumed in the final minute of exercise per kg of body weight) 0-12 weeks: 2.2 (1.0 to 3.4) vs. 2.6 (1.0 to 43) vs. 0.4 (-1.2 to 2.0) vs. 0.4 (-0.9 to 1.7) 26 weeks: 2.0 (0.4 to 3.5) vs. 2.8 (0.8 to 4.8) vs. 1.0 (-0.9 to 3.0) vs. -0.1 (-1.7 to 1.6) *Effect of exercise on functional work capacity* Mean change 0-12 weeks: 2.0 (95% CI 0.60 to 3.49), p=0.00 Mean change 0-26 weeks: 1.9 (95% CI 0.15 to 3.69), p=0.03

Author, year	Employment outcomes	Other outcomes
Wearden, *et al.*, 1998[75]	NR	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
Wearden, *et al.,* 1998[75]	11 medication side-effects (2 reported with placebo)	NR	NR	Unclear, only reported those who dropped out due to AEs	Lansbury Trust	Fair

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
White, *et al.,* 2011[98] ***PACE Trial***	RCT of CBT vs. GET vs. APT vs. usual care for symptoms	**APT vs. CBT vs. GET vs. control** Mean age (SD): 39 (11) vs. 39 (12) vs. 39 (12) vs. 37 (11) years % Female: 76 (121/159) vs. 80 (129/161) vs. 77 (123/160) vs. 76 (122/160) % White: 92 (146/159) vs. 94 (151/161) vs. 93 (148/160) vs. 94 (150/160) % Any depressive disorder: 35 (55/159) vs. 34 (55/161) vs. 34 (54/160) vs. 34 (55/160) % Any psychiatric disorder: 47 (75/159) vs. 47 (75/161) vs. 46 (73/160) vs. 48 (77/160)	Oxford (Sharpe, 1991) criteria **Inclusion:** Bimodal score of ≥6 out of 11 on Chalder fatigue scale and score of ≤60 on SF-36 physical function subscale (after 11 months this was changed to ≤65). **Exclusion:** Ages <18 years, at significant risk of self-harm, unable to attend hospital appointments, unable to speak and read English, had medical needs that made participation inappropriate, had previously received a trial treatment for their present illness at a PACE trial clinic.	**APT vs. CBT vs. GET vs. control** Median (IQR): 33 (16-69) vs. 36 (16-104) vs. 35 (18-67) vs. 25 (15-57) months

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
White, *et al.,* 2011[98] ***PACE Trial***	Number approached: NR Number screened: 3,158 Number eligible: NR Number enrolled: 641 (160 APT, 161 CBT, 160 GET, 160 control) Number analyzed: 630 (159 APT, 155 CBT, 159 GET, 157 control)	United Kingdom 6 specialist CFS clinics	52 weeks	**Overall:** 1.7% (11/641) **APT vs. CBT vs. GET vs. control:** 0.6% (1/160) vs. 3.7% (6/161) vs. 0.6% (1/160) vs. 1.9% (3/160)	NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Interventions	Fatigue outcomes
White, *et al.,* 2011[98] ***PACE Trial***	**Adaptive pacing therapy (APT):** Up to 14 sessions in 23 weeks, with booster session offered at 36 weeks, of individual adaptive pacing therapy with the aim of achieving optimum adaptation to the illness, this was done by helping the participant to plan and pace activity to reduce or avoid fatigue, achieve prioritized activities and provide the best conditions for natural recovery. Strategies consisted of: identifying links between activity and fatigue; encouragement to plan activity to avoid exacerbation; developing awareness of early warnings of exacerbation; limiting demands and stress; regularly planning rest and relaxation; and alternating different types of activities; with advice not to undertake activities that demand >70% of participant's perceived energy envelopes. **CBT:** Up to 14 sessions in 23 weeks, with booster session offered at 36 weeks, of individual CBT with the aim of changing the behavioral and cognitive factors assumed to be responsible for perpetuation of the participant's symptoms and disability. Strategies guided participants to address unhelpful cognitions, including fears about symptoms or activity by testing them in behavioral experiments, consisting of gradual increases in both physical and mental activity. **GET:** Up to 14 sessions in 23 weeks, with booster session offered at 36 weeks, of individual GET with the aim of helping the participant gradually return to appropriate physical activities, reverse the deconditioning, and thereby reduce fatigue and disability. Strategies consisted of establishment of baseline achievable exercise or physical activity, followed by a negotiated, incremental increase in the duration of time spent physically active; target heart rate ranges set when necessary to avoid overexertion; which aimed at 30 minutes of light exercise 5 times a week; with mutually agreed upon gradual increases in intensity and aerobic nature of exercises. **Control:** Usual care.	**APT vs. CBT vs. GET vs. control** *Mean (SD) Chalder fatigue scale scores (0-33 scale, lower scores indicate better health)* 12 weeks: 24.2 (6.4) vs. 23.6 (6.5) vs. 22.8 (7.5) vs. 24.3 (6.5) 24 weeks: 23.7 (6.9) vs. 21.5 (7.8) vs. 21.7 (7.1) vs. 24.0 (6.9) 52 weeks: 23.1 (7.3) vs. 20.3 (8.0) vs. 20.6 (7.5) vs. 23.8 (6.6) Mean difference (95% CI) from control at 52 weeks: -7.0 (-2.3 to 0.9) p=NS vs. -3.4 (-5.0 to -1.8) p=0.0001 vs. -3.2 (-4.8 to -1.7) p=0.0003 vs. NR Mean difference (95% CI) from APT at 52 weeks: NR vs. -2.7 (-4.4 to -1.1) p=0.0027 vs. -2.5 (-4.2 to -0.9) p=0.0059 vs. NR % Improved from baseline (by ≥2 points): 65 (99/153) vs. 76 (113/148) vs. 80 (123/154) vs. 65 (98/152)

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Quality of life outcomes	Function outcomes
White, *et al.,* 2011[98] ***PACE Trial***	NR	**APT vs. CBT vs. GET vs. control** *Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, higher scores indicate better health)* 12 weeks: 41.7 (19.9) vs. 51.0 (20.7) vs. 48.1 (21.6) vs. 46.6 (20.4) 24 weeks: 43.2 (21.4) vs. 54.2 (21.6) vs. 55.4 (23.3) vs. 48.4 (23.1) 52 weeks: 45.9 (24.9) vs. 58.2 (24.1) vs. 57.7 (26.5) vs. 50.8 (24.7) Mean difference (95% CI) from control at 52 weeks: -3.4 (-8.4 to 1.6) p=NS vs. 7.1 (2.0 to 12.1) p=0.0068 vs. 9.4 (4.4 to 14.4) p=0.0005 vs. NR Mean difference (95% CI) from APT at 52 weeks: NR vs. 10.5 (5.4 to 15.6) p=0.0002 vs. 12.8 (7.7 to 17.9) p<0.0001 vs. NR % Improved from baseline (by ≥8 points): 49 (75/153) vs. 71 (105/148) vs. 70 (108/154) vs. 58 (88/152)

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Employment outcomes	Other outcomes
White, *et al.*, 2011[98] ***PACE Trial***	**APT vs. CBT vs. GET vs. control** *Mean (SD) Work and social adjustment scale scores (0-45 scale, lower scores indicate better health)* 52 weeks: 24.5 (8.8) vs. 21.0 (9.6) vs. 20.5 (9.4) vs. 23.9 (9.2); p=0.0001 for CBT vs. control p=0.0006 for GET vs. control; p=0.0001 for CBT vs. APT; p=0.0004 for GET vs. APT	**APT vs. CBT vs. GET vs. control** *Patients with self-rated CGI changes* 12 weeks % Positive change: 13 (20/153) vs. 21 (32/153) vs. 25 (37/151) vs. 5 (7/151) % Minimum change: 82 (126/159) vs. 74 (113/161) vs. 74 (111/151) vs. 88 (133/160) % Negative change: 5 (7/153) vs. 5 (8/153) vs. 2 (3/151) vs. 7 (11/151) 24 weeks % Positive change: 24 (37/155) vs. 38 (56/149) vs. 37 (54/148) vs. 19 (28/151) % Minimum change: 72 (111/155) vs. 55 (82/149) vs. 60 (89/148) vs. 71 (107/151) % Negative change: 5 (7/155) vs. 7 (11/149) vs. 3 (5/148) vs. 11 (16/151) 52 weeks % Positive change: 31 (47/153) vs. 41 (61/147) vs. 41 (62/152) vs. 25 (38/152) % Minimum change: 63 (96/153) vs. 52 (77/147) vs. 53 (80/152) vs. 66 (100/152) % Negative change: 7 (10/153) vs. 6 (9/147) vs. 7 (10/152) vs. 9 (14/152) OR (95% CI) positive change vs. negative change Compared with control: 1.3 (0.8 to 2.1) p=NS vs. 2.2 (1.2 to 3.9) p=0.011 vs. 2.0 (1.2 to 3.5) p=0.013 vs. NR Compared with APT: NR vs. 1.7 (1.0 to 2.7) p=0.034 vs. 1.5 (1.0 to 2.3) p=0.028 vs. NR

Appendix G4. Evidence Table of Included Trials of Interventions for ME/CFS

Author, year	Withdrawals due to adverse event	Serious adverse events	Other adverse events	Total adverse events	Sponsor	Quality rating
White, *et al.,* 2011[98] ***PACE Trial***	NR	**APT vs. CBT vs. GET vs. control** % With ≥1 SAE: 9 (15/159) vs. 4 (7/161) vs. 8 (13/160) vs. 4 (7/160) Number of SAEs: 16 vs. 8 vs. 17 vs. 7 SAEs per 100 person-years (95% CI): 10.1 (5.8 to 16.3) vs. 5.0 (2.2 to 9.8) vs. 10.6 (6.2 to 17.0) vs. 4.4 (1.8 to 9.0) % With ≥1 serious adverse reactions: 1 (2/159) vs. 2 (3/161) vs. 1 (2/160) vs. 1 (2/160) Number of serious adverse reactions: 2 vs. 4 vs. 2 vs. 2 Serious adverse reactions per 100 person-years (95% CI): 1.3 (0.2 to 4.5) vs. 2.5 (0.7 to 6.4) vs. 1.3 (0.2 to 4.5) vs. 1.3 (0.2 to 4.5)	NR	**APT vs. CBT vs. GET vs. control** % With ≥1 non-serious AE: 96 (152/159) vs. 89 (143/161) vs. 93 (149/160) vs. 93 (149/160) Number of non-serious AEs: 949 vs. 848 vs. 992 vs. 977	United kingdom Medical Research Council, Department of Health for England, Scottish Chief Scientist Office, Department for Work and Pensions	Good

ACT= anaerobic activity therapy; ADL= activities of daily living; AE= adverse event; APT= adaptive pacing therapy; BMI= body mass index; CBT= cognitive behavioral therapy; CDC= Centers for Disease Control and Prevention; CFS= chronic fatigue syndrome; CGI= Clinical global impression change score; CI= confidence interval; CIBEROBN= Ventro de Investagacion Biomedica en Red de Fisiopatologia de la Obesidad y Nutricion; CIS= Checklist of individual strength; cm= centimeters; COG= cognitive therapy; DBPC= double blind placebo controlled; DSM-III-R= Diagnostic and Statistical Manual third edition revised; DSM-IV= Diagnostic and Statistical Manual fourth edition; FINE= Fatigue Intervention by Nurses Evaluation; FIQ= Fibromyalgia Impact Questionnaire; FIS= Fatigue Impact Score; FSS= Fatigue Severity Scale; g= gram; GET= graded exercise therapy; HADS= hospital anxiety and depression score; HTA= Health Technology Assessment; IGF1= insulin like growth factor 1; IGFBP3= insulin like growth factor binding protein 3; IgG= immunoglobulin G; IQR= interquartile range; ITT= intention to treat; IV= intravenous; kg= kilogram; KPS= Karnofsky performance score; L= liter; Ltd.= limited; m= meter; ME= Myalgic encephalomyelitis; MFI-20= Multidimensional Fatigue Inventory; mg= milligram; ml= milliliter; mmHG= millimeters mercury; SF-12= Short-form 12-item Health Survey; n= sample size; NHS= National Health Services; NIAID= National Institute of Allergy and Infectious Diseases; NIH= National Institutes of Health; NIHR= National Institute for Health Research; no.= number; NR= not reported; NS= not significant; NSAID= non-steroidal anti-inflammatory drug; OR= odds ratio; PACE= Pacing, graded Activity and Cognitive behavior therapy: a randomized Evaluation; POMS= Profile of Mood States; QLI= Quality of Life Index; QLS= Quality of life scale; QOLI= Quality of Life Inventory; RCT= randomized control trial; SAE= serious adverse event; SD= standard deviation; SEM= standard error of the mean; SF-36= 36-item Short Form Survey; SFQ= Abbreviated fatigue questionnaire; SGR = support the activities of research groups; SIP-8= Sickness Impact Profile 8-item; SSRI= selective serotonin reuptake inhibitor; U.S.= United States; µg= microgram; UK= United Kingdom; vs.= versus; XRCT= cross sectional control trial; ZonMW= ZorgOnderzoek Nederland and Medische wetenschappen.

Appendix H1. Quality Assessment Table of Diagnostic Accuracy/Concordance Studies

Study, Year	Was the test applied to an appropriate spectrum of patients (with and without disease)? Avoid case-control?	Was the population tested consecutive or random?	Adequate sample size?	Eligibility criteria specified? Was there a rigorous assessment of the CFS population?	Reporting of attrition? Minimal loss to followup?
Brown, Evans and Jason, 2013[47]	No - all had CFS but used cluster analysis	Yes - broad-based recruitment, from various sources, consecutive responders	No: n=91 (with adequate data for analysis) 83% female	Unclear/NR	Yes: 20% with incomplete data on the survey
Davenport, *et al.,* 2011[45]	Unclear - CFS group and a non-disabled sedentary control group	Unclear physician referral	No: n=30 100% female	Yes: 2 physicians referred patients meeting criteria	Unclear
Davenport, *et al.,* 2011[46]	Unclear - CFS group and a non-disabled sedentary control group	Unclear physician referral	No: n=30 100% female	Yes: 2 physicians referred patients meeting criteria	Unclear
Gaab, *et al.,* 2004[42]	Unclear - CFS group and a randomly selected control group were matched for age/sex	Unclear for CFS (subjects were recruited from a self-help organization); yes for controls	No: n=42 52% female	Yes: all underwent psychiatric evaluation in addition to fulfilling the CFS criteria	Unclear
Gaab, *et al.,* 2002[43]	Unclear - CFS group and a randomly selected control group were matched for age/sex	Unclear for CFS (subjects were recruited from a self-help organization); yes for controls	No: n=35 43% female	Yes: all underwent psychiatric evaluation in addition to fulfilling the CFS criteria	Unclear
Gaab, *et al.,* 2005[44]	Unclear - CFS group and a randomly selected control group were matched for age/sex	Unclear for CFS (subjects were recruited from a self-help organization); yes for controls	No: n=41 51% female	Yes: all underwent psychiatric evaluation in addition to fulfilling the CFS criteria	Unclear
Hadzi-Pavlovic, *et al.,* 2000[39]	Unclear - CFS controls recruited a non-CFS control	Yes, population-based recruitment of the CFS and control groups	Yes: n=798 66% female	Yes/unclear: assessed diagnostic confidence; analyzed with and without those for whom there was less diagnostic confidence	Yes: began with 770 subjects; final sample 368

Appendix H1. Quality Assessment Table of Diagnostic Accuracy/Concordance Studies

Study, Year	Is the test adequately described and reproducible? Reliable and valid measurements?	Validation of test protocol in a second group?	Standard case definition?	Evaluate all patients for the outcome?	Were the outcome assessors blinded to the reference standard (CFS diagnosis)?	Quality rating
Brown, Evans and Jason, 2013[47]	Yes: used standardized measures	No	No/Unclear Recruited for RCT	No: 91 of 114 had complete data	Unclear	Fair
Davenport, *et al.,* 2011[45]	Yes: described cardiopulmonary exercise tests in detail and it is reproduced from prior studies No reliability/validity results presented	No	Yes: CDC (Fukuda, 1994)	Yes	Unclear	Fair
Davenport, *et al.,* 2011[46]	Yes: used standardized measures	Unclear (reproducibility assessed statistically and construct validity also assessed)	Yes: CDC (Fukuda, 1994)	Yes	Unclear	Fair
Gaab, *et al.,* 2004[42]	Yes: detailed descriptions of salivary cortisol testing No reliability/validity results presented	No	Yes: CFS patients fulfilled both CDC (Fukuda, 1994) and Oxford (Sharpe, 1991) criteria	Yes	Unclear	Fair
Gaab, *et al.,* 2002[43]	Yes: detailed description of insulin tolerance test, ACTH, cortisol No reliability/validity results presented	No	Yes: CFS patients fulfilled both CDC (Fukuda 1994) and Oxford (Sharpe 1991) criteria	Yes	Unclear	Fair
Gaab, *et al.,* 2005[44]	Yes: detailed description of ACTH, cortisol, cytokine No reliability/validity results presented	No	Yes: CFS patients fulfilled both CDC (Fukuda, 1994) and Oxford (Sharpe, 1991) criteria	Yes	Unclear	Fair
Hadzi-Pavlovic, *et al.,* 2000[39]	Yes: used standardized measures	No	Yes: had physician rating of diagnostic confidence regarding CFS diagnosis	No: 92 of 798 subjects were excluded because of incomplete data (70/368 CFS and 22/430 controls)	Unclear	Fair

Appendix H1. Quality Assessment Table of Diagnostic Accuracy/Concordance Studies

Study, Year	Was the test applied to an appropriate spectrum of patients (with and without disease)? Avoid case-control?	Was the population tested consecutive or random?	Adequate sample size?	Eligibility criteria specified? Was there a rigorous assessment of the CFS population?	Reporting of attrition? Minimal loss to followup?
Jason, 2010[40]	Yes - community-based recruitment of CFS population	Yes - recontact of subjects from community-based CFS recruitment	Unclear: n=108 % Female: NR	Yes: 2 physicians independently rated	Yes Loss to follow up: began with 213 from the community sample; data available on 84 without CFS and 24 with CFS
Jason, 2011[41]	Yes - had 2 groups of CFS patients (tertiary care and community sample) and control from community	Yes - community samples recruited from stratified random sample of Chicago neighborhoods; tertiary care CFS group also recruited from variety of sources (physician, newspaper, CFS support groups)	No: n=79 58% female	Yes: 4 physicians and 1 psychiatrist responsible for final decision about diagnosis of community sample; tertiary sample had psychiatric interview	Unclear
Linder, *et al.,* 2002[38]	Yes - CFS population with fibromyalgia and lupus patients as controls	Unclear - recruited by study physicians	Unclear: n=198 68% female	Unclear: few details about how patients were assessed; excluded primary psychiatric disorders	Unclear
Tiev, *et al.,* 2003[37]	Unclear - case-control study; recruitment not reported	Unclear (NR)	No: n=25 64% female	Unclear	Unclear

Appendix H1. Quality Assessment Table of Diagnostic Accuracy/Concordance Studies

Study, Year	Is the test adequately described and reproducible? Reliable and valid measurements?	Validation of test protocol in a second group?	Standard case definition?	Evaluate all patients for the outcome?	Were the outcome assessors blinded to the reference standard (CFS diagnosis)?	Quality rating
Jason, 2010[40]	Used Reeves 2005 criteria as the diagnostic test	No	Yes: screening questionnaire, then DSM-IV interview, medical history/exam and symptom inventory; all met CDC (Fukuda, 1994) criteria	Unclear	Unclear	Fair
Jason, 2011[41]	Yes: used standardized measures	No	Yes: 2 physicians independently rated each file using the CDC (Fukuda, 1994) criteria	Yes	Unclear	Fair
Linder, *et al.,* 2002[38]	Yes: used prospective assessment of 26 symptoms taken from CFS, FMS and SLE diagnostic criteria	Yes: study sample randomly divided into development and validation cohorts	Yes: Oxford (Sharpe, 1991)	Unclear	Unclear	Good
Tiev, *et al.,* 2003[37]	Yes: laboratory test for Rnase L levels described in detail No reliability/validity presented	No	Yes: CDC (Fukuda 1994)	Yes	Unclear	Poor

ACTH = adrenocorticotropic hormone; CDC= Centers for Disease Control and Prevention; CFS= chronic fatigue syndrome; DSM-IV= Diagnostic and Statistical Manual, fourth edition; FMS= fibromyalgia; n= sample size; NR= not reported; RCT= randomized, controlled trial; Rnase L= latent ribonuclease; SLE= systemic lupus erythematosus; UK= United Kingdom.

Appendix H2. Quality Assessment of Randomized, Controlled Trials

Author, year	Randomization adequate?	Allocation con-cealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Bazelmans, *et al.,* 2005[76]	No	No	Yes	Yes	Yes	No	No	No
Blacker, *et al.,* 2004[67]	Yes	NR	Yes	Yes	Yes	Unclear	Unclear	Yes
Blockmans, *et al.,* 2003[69]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes
Burgess, *et al.,* 2012[77]	Yes	Yes	Yes	Yes	Yes	No	No	No
Deale, *et al.,* 1997[78]	Yes	Yes	No	Unclear	Yes	Yes - VAS on fatigue and disability No - all other self-report measures	No	No
Fulcher and White, 1997[106]	Yes	Yes	No	No (exercise group younger)	Yes	Unclear	Unclear	No
Goudsmit, *et al.,* 2009[80]	No	No	No	Unclear	Yes	No	No	No
Ho, *et al.,* 2012[107]	Yes	NR	Yes	Yes	Yes	No	No	No

Appendix H2. Quality Assessment of Randomized, Controlled Trials

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes pre-specified	Funding source	Quality rating
Bazelmans, *et al.,* 2005[76]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	2 (3%) patients excluded from analysis	No	Yes	National Foundation for Public Mental Health (Grant No. 4341)	Fair
Blacker, *et al.,* 2004[67]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Shire Pharmaceutical Development Ltd.	Fair
Blockmans, *et al.,* 2003[69]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	No	Yes	Yes	NR	Fair
Burgess, *et al.,* 2012[77]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	Yes 34% (12/35) vs. 56% (25/45)	Yes	No	Yes	NR	Fair
Deale, *et al.,* 1997[78]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Unclear	No	Yes	South East Thames Regional Health Authority Locally Organized Research Scheme	Fair
Fulcher and White, 1997[106]	Attrition: Yes Crossovers: Yes (22) Adherence: No Contamination: No	No (11%)	Yes	No	Yes	Linbury Trust, a Sainsbury charitable trust	Fair
Goudsmit, *et al.,* 2009[80]	Attrition: No Crossovers: No Adherence: No Contamination: No	NR	NR	No	Yes	Action for ME	Poor
Ho, *et al.,* 2012[107]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	No (19%)	Yes	No	Yes	Center of Behavioral Research fund	Fair

Appendix H2. Quality Assessment of Randomized, Controlled Trials

Author, year	Randomization adequate?	Allocation con-cealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Hobday, *et al.,* 2008[99]	Yes	No	Yes	Yes	Yes	Yes	No	No
Jason, *et al.,* 2007[84]	Yes	NR	Yes	Yes	Yes	Unclear	Unclear	No
Jason, *et al.,* 2010[83]	NR	NR	Yes	Unclear	Briefly	No	No	No
Knoop, *et al.,* 2008[85]	Yes	Yes	Yes	Unclear	Yes	No	No	No
Lopez, *et al.,* 2011[86]	NR	NR	NR	NR	Yes	Unclear	Unclear	No
McKenzie, *et al.,* 1998[68]	Yes	NR	Yes	Yes	Yes	unclear	unclear	Yes
Montoya, *et al.,* 2013[71]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Moss-Morris, *et al.,* 2005[108]	Yes	Yes	No - exercise group younger	No	Yes	Unclear	Unclear	Unclear

Appendix H2. Quality Assessment of Randomized, Controlled Trials

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes pre-specified	Funding source	Quality rating
Hobday, *et al.,* 2008[99]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	Yes (25% of patients did not complete)	No	Yes	Yes	NR	Fair
Jason, *et al.,* 2007[84]	Attrition: No Crossovers: No Adherence: No Contamination: No	NR	Unclear	No	Yes	NIAID (Grant No. AI 49720)	Fair
Jason, *et al.,* 2010[83]	Attrition: No Crossovers: No Adherence: No Contamination: No	NR	NR	No	Yes	National Institute of Allergy and Infectious Diseases (grant numbers AI36295 and AI49720)	Poor
Knoop, *et al.,* 2008[85]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	NR	Fair
Lopez, *et al.,* 2011[86]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	No (ITT not utilized "due to the fact that it was a pilot study")	No	Yes	NIH	Poor
McKenzie, *et al.,* 1998[68]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Unclear	No	Yes	NR	Fair
Montoya, *et al.,* 2013[71]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Hoffman-La Roche (Basel, Switzerland)	Fair
Moss-Morris, *et al.,* 2005[108]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	University of Auckland Staff Grants	**Fair**

Appendix H2. Quality Assessment of Randomized, Controlled Trials

Author, year	Randomization adequate?	Allocation con-cealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Núñez, *et al.,* 2011[87]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	No
Öckerman, 2000[100]	NR	Unclear/NR	Unclear	Unclear	No	Unclear	Yes	Yes
O'Dowd, *et al.,* 2006[88]	Yes	Yes	Yes, except for sex	Unclear	Yes	Yes	No	Yes
Peterson, *et al.,* 1990[70]	Yes	Yes	Yes, except for age	Yes	Yes	Yes	Unclear	Yes
Prins, *et al.,* 2001[89]	Yes	Yes	Yes	No	Yes	No	No	No
Sharpe, *et al.,* 1996[90]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	No
Sutcliffe, *et al.,* 2010[109]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Strayer, *et al.,* 2012[73]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes

Appendix H2. Quality Assessment of Randomized, Controlled Trials

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes pre-specified	Funding source	Quality rating
Núñez, *et al.,* 2011[87]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Unclear	No	Yes	Generalitat of Catalonia, SGR 2009-1158 and CIBEROBN, Carlos III Health Institute, Majadahonda, Madrid	Fair
Öckerman, 2000[100]	Attrition: Yes Crossovers: Yes Adherence: No Contamination: No	No	Yes	No	Yes	NR	Poor
O'Dowd, *et al.,* 2006[88]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: Yes	No/No	Yes	No	Yes	HTA Programme (project NO. 974/41/08)	Fair
Peterson, *et al.,* 1990[70]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Baxter Healthcare Corp.	Fair
Prins, *et al.,* 2001[89]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	Yes/Yes	Yes	Yes	Yes	Health Insurance Council	Fair
Sharpe, *et al.,* 1996[90]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	No	Yes	No	Yes	Wellcome Trust	Good
Sutcliffe, *et al.,* 2010[109]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	Yes (28%)	No	No	Yes	Research grant from the Northern Regional CFS/ME Clinical Network	**Fair**
Strayer, *et al.,* 2012[73]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Hemispherx Biopharma	Fair

Appendix H2. Quality Assessment of Randomized, Controlled Trials

Author, year	Randomization adequate?	Allocation con-cealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Strayer, *et al.,* 1994[72]	Unclear	Yes	Yes, except for sex	Yes	Yes	Yes	Unclear	Yes
Taylor, 2004[91]	Yes	Unclear	Yes	Yes	Yes	No	No	No
The, *et al.,* 2007[101]	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Tummers, *et al.,* 2012[92]	Yes	Yes	Yes	Yes	Yes	No	No	No
Vermeulen and Scholte, 2004[102]	Yes	Yes	Yes	Unclear	Yes	Unclear	No	No
Weatherley-Jones, *et al.,* 2004[104]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Walach, *et al.,* 2008[103]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes (50%) No (50%)
Wearden, *et al.,* 1998[75]	Yes	NR	Yes	Yes	Yes	Yes	Unclear	Yes

Appendix H2. Quality Assessment of Randomized, Controlled Trials

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes pre-specified	Funding source	Quality rating
Strayer, *et al.,* 1994[72]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	No	No	Yes	Hemispherx Biopharma	Fair
Taylor, 2004[91]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	No	Yes	No	Yes	U.S. Department of Education National Institute on Disability and Rehabilitation Research Grant #H133G000097	Good
The, *et al.,* 2007[101]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Grant from Optipharma	Fair
Tummers, *et al.,* 2012[92]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Dutch Medical Research Council ZonMW	Good
Vermeulen and Scholte, 2004[102]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Sigma-Tau Ethifarma Assen	Fair
Weatherley-Jones, *et al.,* 2004[104]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	Yes	No	No	Yes	Linbury Trust	Fair
Walach, *et al.,* 2008[103]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	No	Yes	No	Yes	Maurice Lang Foundation Grant	Good
Wearden, *et al.,* 1998[75]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	Yes	Yes	No	Yes	Linbury Trust	Fair

Appendix H2. Quality Assessment of Randomized, Controlled Trials

Author, year	Randomization adequate?	Allocation con-cealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Wearden, *et al.,* 2010[95] ***FINE Trial***	Yes	Yes	Yes	Yes	Yes	Yes	No	No
White, *et al.,* 2011[98] ***PACE Trial***	Yes	Yes	Yes	Yes	Yes	Yes - statistician No - self-report measures	No	No
Williams, *et al.,* 2002[105]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes

Appendix H2. Quality Assessment of Randomized, Controlled Trials

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes pre-specified	Funding source	Quality rating
Wearden, *et al.,* 2010[95] ***FINE Trial***	Attrition: Yes Crossovers: No Adherence: Yes Contamination: Yes	No	Yes	No	Yes	UK Medical Research Council (G200212) and the UK Department of Health; and the University of Manchester	Good
White, *et al.,* 2011[98] ***PACE Trial***	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	No	Yes	No	Yes	UK Medical Research Council, Department of Health for England, Scottish Chief Scientist Office, Department for Work and Pensions	Good
Williams, *et al.,* 2002[105]	Attrition: Yes Crossovers: No Adherence: Yes Contamination : No	Yes	No	No	Yes	Linbury Trust	Fair

CFS= chronic fatigue syndrome; CIBEROBN= Ventro de Investagacion Biomedica en Red de Fisiopatologia de la Obesidad y Nutricion; Corp.= corporation; FINE= Fatigue Intervention by Nurses Evaluation; HTA= Health Technology Assessment; ITT= intetion-to-treat; Ltd.= limited; ME= myalgic encephalomyelitis; NIAID= National Institute of Allergy and Infectious Diseases; NIH = National Institutes of Health; No.= number; NR= not reported; PACE= Pacing, graded Activity and Cognitive behavior therapy: a randomized Evaluation; SGR= support the activities of research groups; U.S.= United States; UK= United Kingdom; VAS= visual analogue scale; vs.= versus; ZonMW= ZorgOnderzoek Nederland and Medische wetenschappen.

Appendix I. Published Case Definition Criteria

Case Definition Statements	General Diagnostic Criteria	Fatigue	Post-Exertional Malaise	Sleep
CDC, Holmes, *et al.,* 1988[6]	Requires each of the following: 1. New onset of ≥6 months of persistent or relapsing, debilitating fatigue not resolved with bed rest 2. ≥8 of the symptom criteria, or 6 of the symptom criteria + ≥2 of following: low grade fever, nonexudative pharyngitis, palpable, or tender lymph nodes 3. ≥50% impairment of daily functioning as compared to premorbid levels	6-8 of the symptoms in any category: generalized fatigue after levels of exercise that would have been easily tolerated previously	None noted	6-8 of the symptoms in any category: Sleep disturbance
Oxford Sharpe, *et al.,* 1991[49] CFS	Requires each of the following: 1. Fatigue as principal symptom 2. Definite onset of syndrome (not lifelong) 3. Syndrome must be severe, disabling have an effect on physical and mental (cognitive) functioning; 4. Present for >6 months, or >50% of the time 5. May include other symptoms: myalgias, mood and sleep disturbance	Fatigue is required to be complained of, significantly affect the patient's functioning, be disproportionate to exertion, represent a clear change from a previous state and be present >50% of the time.	None noted	Sleep disturbances are required to be complained of, not a response to external disturbances, changes from previous states, and persistent.
London Dowsett, *et al.,* 1994[50] ME/CFS	Must meet all 3 criteria: 1. Exercise-induced fatigue, see fatigue criteria. 2. Impairment of short-term memory and loss of powers of concentration, usually coupled with other neurological and psychological disturbances, see neurologic/cognitive criteria. 3. Fluctuation of symptoms, usually precipitated by either physical or mental exercise.	Exercise-induced fatigue precipitated by trivially small exertion (physical or mental) relative to the patient's previous exercise tolerance.	Nothing noted	Nothing noted
CDC ≥6 months Fukuda, *et al.,* 1994[3] CFS	2 of the fatigue criteria and ≥4 of the criteria in any category	Unexplained, persistent fatigue ≥6 months not due to ongoing exertion, not substantially relieved by rest, of new onset, and results in a significant reduction in previous activity levels.	Post-exertional malaise	Unrefreshing sleep

Appendix I. Published Case Definition Criteria

Case Definition Statements	Pain	Neurological/cognitive
CDC, Holmes, *et al.,* 1988[6]	6-8 of the symptoms in any category: Myalgia Migratory arthralgia without joint swelling or redness Painful lymph notes Muscle discomfort	6-8 of the symptoms in any category: Neuropsychological complaints Prolonged (>24 hours) generalized headaches
Oxford Sharpe, *et al.,* 1991[49] CFS	Myalgia should be complained of, disproportionate to exertion, a change from a previous state, persistent or recurrent, and should be distinguished from joint pain or weakness.	Mood disturbances should be complained of, significant changes from previous state and should be relatively persistent or recurrent. This may include depression, loss of interest or pleasure, anxiety, emotional liability or irritability.
London Dowsett, *et al.,* 1994[50] ME/CFS	Nothing noted	Impairment of short-term memory and loss of powers of concentration, usually coupled with other neurological and psychological disturbances such as emotional lability (being upset by things that would not normally cause distress), nominal dysphasia (difficulty finding the right word), disturbed sleep patterns, dysequilibrium (imbalance or unsteadiness rather than vertigo/spinning round) or tinnitus (noises in the ear).
CDC ≥6 months Fukuda, *et al.,* 1994[3] CFS	Muscle pain Multi-joint pain without swelling or redness Headaches of new type or severity Recurrent sore throat Tender cervical or axillary lymph nodes	Impaired memory of concentration

Appendix I. Published Case Definition Criteria

Case Definition Statements	Other Criteria	Additional Considerations
CDC, Holmes, *et al.,* 1988[6]	6-8 of the symptoms in any category: Mild fever, sore throat, or description of the main symptom complex as initially developing over a few hours to a few days	None
Oxford Sharpe, *et al.,* 1991[49] CFS	Disability refers to any restriction or lack of ability to perform an activity within the range considered normal for a human being, it should be distinguished from impairment of function and handicap.	None
London Dowsett, *et al.,* 1994[50] ME/CFS	Fluctuation of symptoms, usually precipitated by either physical or mental exercise.	None
CDC ≥6 months Fukuda, *et al.,* 1994[3] CFS	Recurrent sore throat Tender cervical or axillary lymph nodes	Diagnosis of CFS-like illness if ≥6 months fatigue but doesn't meet other criteria

Appendix I. Published Case Definition Criteria

Case Definition Statements	General Diagnostic Criteria	Fatigue	Post-Exertional Malaise	Sleep
Canadian ≥ 6 months Carruthers, *et al.,* 2003[1] ME/CFS	All of the following: Fatigue Post-exertional fatigue Sleep dysfunction Pain ≥2 of the following: Neurological/cognitive manifestations ≥1 symptoms from ≥2 of the following categories: Autonomic Neuroendocrine Immune	New onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.	Loss of physical and mental stamina, rapid muscular and cognitive fatigability, post-exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a slow recovery period, usually ≥24 hours.	Unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms.*
Reeves, *et al.,* 2005[48] CFS	Follows Fukuda, 1994 criteria, meant to define how to apply criteria	Fatigue (must satisfy all): - Lasting >6 months - Not relieved by rest (by answering "a little or not at all" to the question "is your fatigue relieved by rest?) - Causing substantial reduction in occupational, educational, social, or recreational activities (by answering "a lot" to "Does fatigue interfere with...") Severe fatigue as >medians of the MFI-20 general fatigue (>13) or reduced activity (>10) scales.	Nothing noted	Nothing noted

Appendix I. Published Case Definition Criteria

Case Definition Statements	Pain	Neurological/cognitive
Canadian ≥ 6 months Carruthers, *et al.,* 2003[1] ME/CFS	Significant myalgia and/or arthralgia, is often widespread and migratory in nature. Often there are significant headaches of new type, pattern or severity.**	≥2 of the following: Confusion, impaired concentration and short-term memory, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances (e.g., spatial instability and disorientation and inability to focus vision). Ataxia, muscle weakness and fasciculations are common. There may be overload phenomena: cognitive, sensory (e.g., photophobia and hypersensitivity to noise); and/or emotional overload, which may lead to crash periods and/or anxiety.
Reeves, *et al.,* 2005[48] CFS	Nothing noted	Nothing noted

Appendix I. Published Case Definition Criteria

Case Definition Statements	Other Criteria	Additional Considerations
Canadian ≥ 6 months Carruthers, *et al.,* 2003[1] ME/CFS	≥1 symptoms from ≥2 of the following categories: 1. Autonomic manifestations: orthostatic hypotension, neurally mediated, postural orthostatic tachycardia syndrome, delayed postural hypotension; light-headedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnea. 2. Neuroendocrine manifestations: loss of thermostatic stability. subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change. anorexia or abnormal appetite; loss of adaptability and worsening of symptoms with stress. 3. Immune manifestations: tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals.	*There is a small number of patients who have no pain or sleep dysfunction, but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS can be entertained when this group has an infectious illness type onset. **Some patients have been unhealthy for other reasons prior to the onset of ME/CFS and lack detectable triggers at onset and/or have more gradual or insidious onset.
Reeves, *et al.,* 2005[48] CFS	-Presence of 4 of 8 case-defining symptoms (by answering "all of the time or most of the time" to questions about symptoms, e.g. "during the past month how often have you had a sore throat?)" '-Functional impairment defined as score <25th percentile of the SF-36 on the physical function (<70), or role physical (<50), or social function (<75), or role emotional (<66.7) '-Reporting >4 symptoms and scoring >25 on the Symptom Inventory Case Definition Subscale	None

Appendix I. Published Case Definition Criteria

Case Definition Statements	General Diagnostic Criteria	Fatigue	Post-Exertional Malaise	Sleep
Revised Canadian ≥6 months Jason, *et al.,* 2010[51] ME/CFS	All of the following : ≥ 6 months of persistent fatigue Post-exertional malaise and/ or post-exertional fatigue Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance ≥1 of myofascial and/or joint pain ≥2 neurological/cognitive manifestations ≥1 symptom from 2 of the following 3 categories: 1. Autonomic manifestations, 2. Neuroendocrine manifestations 3. Immune manifestation	≥6 months, persistent or recurring chronic fatigue that is not lifelong and results in substantial reductions in previous levels of occupational, educational, social, and personal activities.	Post-exertional malaise and/ or post-exertional fatigue. With activity there must be a loss of physical or mental stamina, rapid/sudden muscle or cognitive fatigability, post-exertional malaise and/or fatigue and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. The recovery is slow, often taking 2-24 hours or longer.	Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance. May include unrefreshing sleep, prolonged sleep (including frequent naps), disturbed sleep (e.g., inability to fall asleep or early awakening) and/or day/night reversal.

Appendix I. Published Case Definition Criteria

Case Definition Statements	Pain	Neurological/cognitive
Revised Canadian ≥6 months Jason, *et al.,* 2010[51] ME/CFS	Pain (or discomfort) that is often widespread and migratory in nature. <u>≥1 symptom from any of the following:</u> Myofascial and/or joint pain, myofascial pain can include deep pain, abdomen/stomach pain, or achy and sore muscles. Pain, stiffness, or tenderness may occur in any joint but must be present in ≥1 joint and lacking edema or other signs of inflammation. Abdominal and/or head pain. May experience stomach pain or chest pain. Headaches often described as localized behind the eyes or in the back of the head. May include headaches localized elsewhere, including migraines. Headaches would need to be more frequent than they were before, which would indicate new pattern, of a new type as compared to headaches previously experienced, or different in severity type as compared to headaches previously experienced by the patient.	<u>≥2 neurological/cognitive manifestations:</u> Impaired memory (self-reported or observable disturbance in ability to recall information or events on a short-term basis); difficulty focusing vision and attention (disturbed concentration may impair ability to remain on task, to screen out extraneous/excessive stimuli); loss of depth perception; difficulty finding the right word; frequently forget what wanted to say; absent mindedness; slowness of thought; difficulty recalling information; need to focus on one thing at a time; trouble expressing thought; difficulty comprehending information; frequently lose train of thought; sensitivity to bright lights or noise; muscle weakness/muscle twitches

Appendix I. Published Case Definition Criteria

Case Definition Statements	Other Criteria	Additional Considerations
Revised Canadian ≥6 months Jason, *et al.,* 2010[51] ME/CFS	≥1 symptom from 2 of the following 3 categories: 1. Autonomic manifestations: neurally mediated hypotension, postural orthostatic tachycardia, delayed postural hypotension, palpitations with or without cardiac arrhythmias, dizziness or fainting, feeling unsteady on the feet--disturbed balance, shortness of breath, nausea, bladder dysfunction, or irritable bowel syndrome. 2. Neuroendocrine manifestations recurrent feelings of feverishness and cold extremities, subnormal body temperature and marked diurnal fluctuations, sweating episodes, intolerance of extremes of heat and cold, marked weight change-loss of appetite or abnormal appetite. 3. Immune manifestations: recurrent flu-like symptoms, non-exudative sore or scratchy throat, repeated fevers and sweats, lymph nodes tender to palpitation--generally minimal swelling noted, new sensitivities to food, odors, or chemicals.	None

Appendix I. Published Case Definition Criteria

Case Definition Statements	General Diagnostic Criteria	Fatigue	Post-Exertional Malaise	Sleep
International Consensus Statement Carruthers, *et al.,* 2011[2] ME	A. Post-exertional neuroimmune exhaustion: cardinal B. Neurological impairments ≥ 1 from 3 of the 4 symptom categories: 1. Neurocognitive impairments 2. Pain 3. Sleep disturbance 4. Neurosensory, perceptual, and motor disturbances C. Immune, gastrointestinal, and genitourinary impairments ≥1 symptom from ≥3 of the following: 1.Flu-like symptoms 2. Susceptibility to viral infections 3.Gastrointestinal symptoms 4.Gentourinary symptoms 5. Sensitivities to food, medications, odors or chemicals D. Energy production⁄transportation impairments: ≥1 1. Cardiovascular – orthostatic, etc. 2. Respiratory – shortness of breath, etc. 3. Thermostatic instability 4. Temperature intolerance	≥1 Symptom: 1. Cardiovascular: e.g. inability to tolerate an upright position - orthostatic intolerance, neurally mediated hypotension, postural orthostatic Tachycardia syndrome, palpitations with or without cardiac arrhythmias, light-headedness⁄dizziness 2. Respiratory: e.g. air hunger, labored breathing, fatigue of chest wall muscles 3. Loss of thermostatic stability: e.g. subnormal body temperature, marked diurnal fluctuations; sweating episodes, recurrent feelings of feverishness with or without low grade fever, cold extremities 4. Intolerance of extremes of temperature	1. Marked, rapid physical and⁄or cognitive fatigability in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse 2. Post-exertional symptom exacerbation: e.g. acute flu-like symptoms, pain and worsening of other symptoms. 3. Post-exertional exhaustion may occur immediately after activity or be delayed by hours or days. 4. Recovery period is prolonged, usually taking 24 hour longer. A relapse can last days, weeks or longer. 5. Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level.	≥1 from Sleep, Pain, or Neurological/cognitive categories: Disturbed sleep patterns: e.g. insomnia, prolonged sleep including naps, sleeping most of the day and being awake most of the night, frequent awakenings, awaking much earlier than before illness onset, vivid dreams ⁄nightmares b. Unrefreshed sleep: e.g. awaken feeling exhausted regardless of duration of sleep, day-time sleepiness

Appendix I. Published Case Definition Criteria

Case Definition Statements	Pain	Neurological/cognitive
International Consensus Statement Carruthers, *et al.,* 2011[2] ME	≥1 from Sleep, Pain, or Neurological/cognitive categories: Headaches: e.g. chronic, generalized headaches often involve aching of the eyes, behind the eyes or back of the head that may be associated with cervical muscle tension; migraine; tension headaches b. Significant pain can be experienced in muscles, muscle-tendon junctions, joints, abdomen or chest. It is non-inflammatory in nature and often migrates. e.g. generalized hyperalgesia, widespread pain (may meet fibromyalgia criteria), myofascial or radiating pain	≥1 from Sleep, Pain, or Neurological/cognitive categories: 1. Neurocognitive impairments: a. Difficulty processing information: slowed thought, impaired concentration e.g. confusion, disorientation, cognitive overload, difficulty with making decisions, slowed speech, acquired or exertional dyslexia b. Short-term memory loss: e.g. difficulty remembering what one wanted to say, what one was saying, retrieving words, recalling information, poor working memory 2. Neurosensory, perceptual and motor disturbances a. Neurosensory and perceptual: e.g. inability to focus vision, sensitivity to light, noise, vibration, odor, taste and touch; impaired depth perception b. Motor: e.g. muscle weakness, twitching, poor coordination, feeling unsteady on feet, ataxia

Appendix I. Published Case Definition Criteria

Case Definition Statements	Other Criteria	Additional Considerations
International Consensus Statement Carruthers, *et al.*, 2011[2] ME	Immune, gastrointestinal and genitourinary impairments; ≥1 symptom from ≥3 of the following: 1. Flu-like symptoms typically worsen with exertion e.g. sore throat, sinusitis, cervical and/or axillary lymph nodes may enlarge or be tender on palpitation 2. Susceptibility to viral infections with prolonged recovery periods 3. Gastro-intestinal tract: e.g. nausea, abdominal pain, bloating, irritable bowel syndrome 4. Genitourinary: e.g. urinary urgency or frequency, nocturia 5. Sensitivities to food, medications, odors or chemicals	None

CDC= Centers for Disease control and Prevention; CFS= chronic fatigue syndrome; e.g.= example; etc.= etcetera; ME= myaligic encephalomyelitis; MFI-20= Multidimensional Fatigue Inventory, 20-item; NR= not reported; SF-36= 36-item Short Form Survey.

Appendix J. Standardized Measures Tables

Table 1. Standardized measures used in evaluation of case definitions of ME/CFS

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Beck Depression Inventory[1]	BDI	Self-reported multiple-choice inventory of 21-questions for measuring the severity of depression. Scores of 0-9 indicate minimal depression, 10-18 mild depression, 19-29 moderate depression, 30-63 severe depression.	Validated in population receiving treatment for CFS[2]
Brief Coping Orientation to Problems Experienced Scale[3]	bCOPE	28 questions that cover 14 coping strategies as potential responses to stressors: self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-blame. Each item scored on 1-4 scale (1=haven't been doing this at all and 4=have been doing this a lot), each coping strategy is scored 2-8.	None
Chronic Fatigue Syndrome Medical Questionnaire[4]		Single item of questionnaire: rate the severity of your post-exertional malaise over the past 6 months using scale of 0-100, with lower scores indicating less severity.	Developed for CFS population
Chronic Fatigue Symptoms Checklist[5,6] – Lloyd et al. 1990 Br J Psychiatry156:534-540.	CFSC	Self-reported set of 40 symptoms, 30 thought to be typical of CFS symptoms and 10 considered atypical. Each item is scored 0-4, with 0=never suffer from it; 1=mild or rare symptoms during the last month causing minor disruption; 2=moderate or frequent symptoms during the last month causing major disruption; 3=severe or very frequent symptoms during the last month unable to perform usual activities; and 4=suffered from it previously for ≥1 month but not now.	Designed for CFS patients
Cognitive Failures Questionnaire[7]	CFQ	The CFQ measure self-reported failures in perception, memory and motor function over the previous 6-months. It consists of 25 items, each graded on a scale of 5 point Likert-scale, total scores are calculated by adding the individual item scores. Final scores range from 0-100, lower scores indicate better health.	None
Fatigue Impact Scale [8]	FIS	Self- reported instrument of fatigue impact on 40-items subdivided into 3 subscales, cognitive functioning (10-items), physical functioning (10-items, and psychosocial functioning (20-items). Each item is rated from 0 (no problem) to 4 (extreme problem), with a maximum score of 160.	Validated in population who had experienced ≥6 months of fatigue[8]
General Health Questionnaire[9]	GHQ	A 60-item questionnaire to screen individuals for psychiatric disorders, scores are given as means and scores above 3 indicate disorders; a 30-item version of the same questionnaire uses a threshold of 6 to indicate general psychological distress.	None
Hospital Anxiety and Depression Scale[10]	HADS	Self-reported scale of 14-items for the detection of depression and anxiety in hospitalized patients. Scores range from 1-21 interpreted as: normal (0-7), mild (8-10), moderate (11-14), severe (15-21). Subscales for anxiety (HADS-A) and depression (HADS-D).	Validated in patients identified using CDC (Fukuda, 1994) criteria[11]

Appendix J. Standardized Measures Tables

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Karnofsky Performance Scale[12]	KPS	Descriptive ordinal scale that measures the patient's ability to carry on normal activities/the degree of assistance required. The scale range is comprised of 10-point intervals from 0-100, where 0=dead and 100=normal, no complaints or evidence of disease. Score thresholds: 80-100=normal health; 50-80=an inability to work, with a varying amount of assistance needed at home; 10-40=an inability for self care requiring the equivalence of institutional care	Validated in patients with chronic pain, but not specifically CFS[13]
Multidimensional Fatigue Inventory[14]	MFI-20	Self-reported instrument used to measure fatigue consisting of 5 subscales: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Each subscale has 4 statements regarding levels of fatigue experienced in the previous days (20 total) rated on a Likert-type scale from 1-5 for a final subscale score of 4-20, lower scores indicate less fatigue.	Validated in those with >12 months of fatigue[14] Validated in population self-reporting symptoms meeting CDC (Fukuda, 1994) criteria[15]
Modified Somatic Perception Questionnaire[16]	MSPQ	Self-reported 13-item scale for patients with chronic pain or disabilities, it is used to identify somatic complaints that may be associated with psychological responses such as anxiety or depression. Each item is scored 0-3 (0=not at all and 3=extremely could not have been worse) for a total score of 0-39 with lower scores indicated lower general somatic symptoms.	None
Orthostatic Grading Scale[17]	OGS	Self-reported 5-item scale assessing for symptoms of orthostatic intolerance because of orthostatic hypotension. Each item is scored 0-4, with total score of 0-20, with lower scores indicated better health.	None
Pennebaker Inventory of Limbic Languidness[18]	PILL	Self-reported 54-item questionnaire measures the tendency for someone to notice and report a broad array of physical symptoms and sensations. Each item scored from 0-4 (0=never or almost never experienced and 4=more than once a week) for a total score of 0-216 interpreted as: 0-21 below normal range; 22-66 well within normal range; 67-84slighly above average, within normal range; and ≥85 top 25%.	None
Sickness Impact Profile 8-items[19,20]	SIP-8	Self-reported measure of perceived impact of illness or disease on physical and psychosocial functioning, it can be self or interviewer administered. The 8 subscales used are home management, mobility, alertness behavior, sleep/rest, ambulation, social interactions, work and recreation and pastimes. A total score is calculated by addition of the weights of items (range 0–5,799). Lower scores indicate better health.	None
36-item Short Form survey[21]	SF-36	Self-reported survey of 36 questions of patient health on 8 subscales: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The scale has a range from 0-100, with higher scores indicating better health.	Validated in those identified using CDC (Holmes, 1988) criteria[22,23]
Somatization Checklist [24]	None	Self-reported set of 39 physical symptoms derived from diagnostic interview schedule for making a DSM-III/III-R diagnosis of somatization disorder. Items were answered yes or no for current and lifetime symptoms.	None

Appendix J. Standardized Measures Tables

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Symptom Checklist-90[25]	SCL-90	Self-reported checklist of 90 questions to assess psychological status in the following categories: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism.	None
Zung Self-Rating Depression Scale[26]	ZDS	Self-reported questionnaire of 20-items that rate affective, psychological, and somatic symptoms associated with depression. Each item is rated from 1 (a little of the time) to 4 (most of the time) with final scores ranging from 20-80, interpreted as: 20-44 normal, 45-59 mildly depressed, 60-69 moderately depressed, ≥70 severely depressed.	None

BDI = Beck Depression Inventory; bCOPE = brief Coping Orientation to Problems Experienced scale; CDC = Centers for Disease Control and Prevention; CFS = Chronic Fatigue Syndrome; CFSC = chronic fatigue symptoms checklist; CFQ= Cognitive Failures Questionnaire; DSM III/III-R= Diagnostic and Statistical Manual third edition/third edition revised; GHQ = General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; HADS-A = anxiety subscale of HADS; HADS-D = depression subscale of HADS; KPS = Karnofsky Performance Scale; MFI-20 = Multidimensional Fatigue Inventory 20-Item; MSPQ = Modified Somatic Perception Questionnaire; PILL= Pennebaker Inventory of Limbic Languidness; SIP-8 = Sickness Impact Profile 8-Item; SF-36 = Short Form-36; SCL-90 = Symptom Checklist; ZDS = Zung Self-Rating Depression Scale.

Appendix J. Standardized Measures Tables

Table 2. Standardized measures used to assess outcomes after interventions for ME/CFS

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Abbreviated Fatigue Questionnaire[27]	SFQ	Self-reported measure of fatigue consisting of 4 questions answered on a 7-point Likert-type scale. Final scores range from 4-28, with higher scores indicate lower levels of fatigue.	None
Clinical global impression change score[28]	CGI	Clinician-rated clinical global impression of change. Levels of improvement after intervention is rated on a 7 point Likert-type scale where 1=very much better and 7=very much worse. Note: Several studies had the patients self-report their ratings instead of a clinician.	None
Chalder Fatigue Scale[29]	None	Self-reported, 14- or 11-item fatigue scale. Items scored dichotomously on a 4-point scale (0,0,1,1), lower scores indicate better outcomes, total scores ≥4 designate clinically significant levels of fatigue. Note: Several different scoring methods are used for this scale.	Validated in those identified using Oxford (Sharpe, 1991) criteria[30] Validated in CFS patient meeting either Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) criteria[31]
Checklist of Individual Strength[19]	CIS	Self-reported questionnaire measuring several aspects of fatigue, 20-items, separated into 4 subscales: severity of fatigue (8-items), concentration problems (5-items), decrease motivation (4-items), and decreased physical activity (3-items). Each item is rated on a 7-point Likert-type scale for final scores of 20- 140. Lower scores indicate better health.	Validated in patients with >1 year self-reported fatigue unexplained by other diagnosis[19]
EuroQol Scale [32]	None	Measures health status, with scores ranging from 0=worst health status to 100=best health status.	Validated in population meeting Oxford (Sharpe, 1991) criteria[33]
Fatigue Impact Scale [8]	FIS	Self- reported instrument of fatigue impact on 40-items subdivided into 3 subscales, cognitive functioning (10-items), physical functioning (10-items, and psychosocial functioning (20-items). Each item is rated from 0 (no problem) to 4 (extreme problem), with a maximum score of 160.	Validated in population who had experienced ≥6 months of fatigue[8]
Fatigue Severity Scale[34]	FSS	Self-reported measure of fatigue, composed of 9-items rated on 7-point Likert-type scales, where 1=no fatigue-related impairment and 7=high impairment. Final scores range from 9-63, lowers scores indicate lower fatigue impairment.	Validated in patients with CFS like symptoms, but not formally diagnosed[35]
Fibromyalgia Impact Questionnaire[36]	FIQ	Self-reported 10-item measure that assesses the current health status of patients with fibromyalgia on physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and wellbeing. Each item has multiple questions scored on Likert-type scales, for a final score ranging from 0-100. Lower scores indicate better health.	None

Appendix J. Standardized Measures Tables

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Karnofsky Performance Scale[12]	KPS	Descriptive ordinal scale that measures the patient's ability to carry on normal actives/the degree of assistance required. The scale range is comprised of 10-point intervals from 0-100, where 0=dead and 100=normal, no complaints or evidence of disease. Score thresholds: 80-100=normal health; 50-80=an inability to work, with a varying amount of assistance needed at home; 10-40=an inability for self care requiring the equivalence of institutional care	Validated in patients with chronic pain, but not specifically CFS[13]
Medical Outcome Study Short Form[37]	MOS-SF	Measures functioning and well being of 6 health concepts: physical functioning, social functioning role functioning, mental health, health perceptions, and bodily pain. Each area has varying numbers of items and are scored on scales from 1-100, with higher scores indicating better health.	Validated in patients with chronic conditions[38] Validated in those identified using Oxford (Sharpe, 1991) criteria[39]
Modified barthel's Activities of Daily Living index[40]	ADL	Self-reported measure that measures the patient's ability to preform 83 discrete activities of daily living. The maximum score is 100, higher scores indicate better health.	None
Multidimensional Fatigue Inventory[14]	MFI-20	Self-reported instrument used to measure fatigue consisting of 5 subscales: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Each subscale has 4 statements regarding levels of fatigue experienced in the previous days (20 total) rated on a Likert-type scale from 1-5 for a final subscale score of 4-20, lower scores indicate less fatigue.	Validated in those with >12 months of fatigue[14] Validated in population self-reporting symptoms meeting CDC (Fukuda, 2004) criteria[15]
Profile of Mood States[41]	POMS	Self-reported scale used to assess transient mood states, consisting of 65 adjectives, separated into 6 subscales: tension-anxiety, depression-dejection, anger-hostility, fatigue, vigor, confusion. Each item is rated on a 5-point Likert-type scale, items for the subscales are combined with vigor scores subtracted for an overall score ranging from 0-200. For this review, only the fatigue and vigor subscales were included. The maximum score for the fatigue subscale is 28, and the maximum score for the vigor subscale is 32.	None

Appendix J. Standardized Measures Tables

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Quality of Life Index[42,43]	QLI	Self-reported questionnaire covering 34-items related to quality of life overall and in 4 subscales: health and functioning, social and economic, psychological/spiritual, and family. The first part of the questionnaire rates satisfaction with 34-items on a 6-point Likert-type scale ranging from very dissatisfied to very satisfied (-2.5 to 2.5 for analysis). The second part of the questionnaire rates the importance of these items from 1=very unimportant to 6=very important. Final scores for each subscales and the total scale range from 0-30 and are computed by weighting satisfaction responses with paired importance responses. Higher scores indicate higher life quality.	Used in CFS populations, but unclear if validated[44]
Quality of Life Inventory[45,46]	QOLI	Inventory of patient satisfaction and happiness in 17 (16 in the more recent version) areas of life potentially relevant to overall life satisfaction. Each area is first rated in terms of importance to overall happiness where 0=not at all important, 1=important, and 2=very important. The items are then rated in terms of the patient satisfaction with that area on a scale ranging from -3 (very dissatisfied) to 3 (very satisfied). The 2 scores are multiplied to produce weighted satisfaction ratings ranging from -6 to 6 and the overall life satisfaction score is obtained by averaging all weighted satisfaction ratings that have nonzero importance ratings. Higher scores indicate better health.	None
Quality of Life Scale[47]	QLS	16-items answered on a 7-point Likert-type scale which measures 6 conceptual domains of quality of life: material and physical well-being; relationships with other people; social, community and civic activities; personal development and fulfillment; recreation; and independence. Scored on a 16-113 scale, higher scores indicate better quality of life.	None
36-item Short Form Survey [21]	SF-36	Self-reported survey of 36 questions of patient health on 8 subscales: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The scale has a range from 0-100, with higher scores indicating better health. For this review, only the physical functioning and vitality subscales were included.	Validated in those identified using CDC (Holmes, 1988) criteria[22,23]
Short Form 12-Item Health Survey[48]	SF-12	A health survey with 12-items assessing physical and mental health. The survey yields 2 summary scores: the mental component summary and the physical component summary. Each summary score ranges from 0-100, higher scores indicate better health.	None
Sickness Impact Profile 8-items [19,20]	SIP-8	Self-reported measure of perceived impact of illness or disease on physical and psychosocial functioning, it can be self or interviewer administered. The 8 subscales used are home management, mobility, alertness behavior, sleep/rest, ambulation, social interactions, work and recreation and pastimes. A total score is calculated by addition of the weights of items (range 0–5,799). Lower scores indicate better health.	None

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Work and social adjustment scale[49]	None	A 5-item questionnaire that measures impairment in in work, home management, social activities, and private leisure. Each item is measured on a 0-8 Likert-type scale where 8=maximum impairment. The scale is scored from 0-45.	Validated in CFS populations receiving treatment[50]

ADL = Activities of Daily Living; CDC= Centers for Disease Control and Prevention; CFS= chronic fatigue syndrome; CGI= Clinical Global Impression Change Score; CIS= Checklist of Individual Strength; FIQ= Fibromyalgia Impact Questionnaire; FIS= Fatigue Impact Scale; FSS= Fatigue Severity Scale; KPS = Karnofsky Performance Scale; MFI-20=Multidimensional Fatigue Inventory; POMS= Profile of Mood States; QLI= Quality of Life Index; QLS= Quality of Life Scale; QOLI= Quality of Live Inventory; SF-36= Short Form-36; SF-12= Short-Form 12-Item Survey; SFQ= Abbreviated Fatigue Questionnaire; SIP-8= Sickness Impact Profile 8 items. Medication

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Appendix K. Strength of Evidence Table

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
KQ2a. What are the benefits of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?								
Galantamine vs. placebo								
Decreased fatigue	1 RCT (n=423)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life	1 RCT (n=423)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Global improvement	1 RCT (n=423)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved overall function, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Hydrocortisone vs. placebo								
Improved overall function	1 RCT (n=68)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=68)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life	1 RCT(n=65)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Hydrocortisone + fludrocortisone vs. placebo								
Improved overall function	1 RCT (n=80)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=80)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life	1 RCT (n=80)	Medium	Direct	Consistency unknown	Imprecise	Undetected	<>	Insufficient

Appendix K. Strength of Evidence Table

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
				(single study)				
Increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Immunoglobulin G vs. placebo								
Improved overall function	1 RCT (n=28)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Decreased fatigue, improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Rintatolimod vs. placebo								
Improved overall function	1 RCT (n=84)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Increased exercise capacity	2 RCT (n=316)	Medium	Direct	Consistent	Precise	Undetected	+	Low
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Valganciclovir vs. placebo								
Improved overall function	1 RCT (n=30)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=30)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Isoprinosine vs. placebo								
Improved overall function	1 RCT (n=15)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=15)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient

Appendix K. Strength of Evidence Table

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Fluoxetine vs. placebo								
Improved overall function	1 RCT (n=68)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=68)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
CBT/counseling vs. no treatment or support or relaxation or adaptive pacing								
Improved overall function	12 RCT (n=1,637) 8 pooled	Medium	Direct	Inconsistent	Precise	Undetected	SF-36 physical function WMD 7.73 (95% CI, 3.58 to 11.87)	Low
Decreased fatigue	12 RCT (n=1,635)	Medium	Direct	Consistent	Precise	Undetected	+[†]	Moderate
Improved quality of life	5 RCT (n=539)	Medium	Direct	Consistent	Imprecise	Undetected	<>[‡]	Low
Increased proportion working full- or part-time	2 RCT (n=145)	Medium	Direct	Consistent	Imprecise	Undetected	<>	Low
Increased hours worked	3 RCT (n=321)	Medium	Direct	Inconsistent	Imprecise	Undetected	<>[§]	Low
Decreased work impairment	2 RCT (n=531)	Medium	Direct	Consistent	Precise	Undetected	+	Low
Global improvement	3 RCT (n=727)	Medium	Direct	Consistent	Precise	Undetected	+	Moderate
Acclydine vs. placebo								
Improved overall function	1 RCT (n=57)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient

Appendix K. Strength of Evidence Table

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Decreased fatigue	1 RCT (n=57)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Increased physical activity (actometer)	1 RCT (n=57)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination								
Decreased fatigue	1 RCT (n=89)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Global improvement	1 RCT (n=89)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved overall function and quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Pollen extract vs. placebo								
Decreased fatigue	1 RCT (n=22)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved quality of life	1 RCT (n=22)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved overall function, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Low sugar/low yeast diet vs. healthy eating								
Decreased fatigue	1 RCT (n=39)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life	1 RCT (n=39)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient

Appendix K. Strength of Evidence Table

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Improved overall function, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Distant healing vs. no treatment								
Improved overall function	1 RCT (n=409)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>[ll]	Insufficient
Decreased fatigue, improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Homeopathy vs. placebo								
Improved overall function	1 RCT (n=89)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=89)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	-	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Melatonin vs. phototherapy								
Improved overall function	1 RCT crossover design (n=30)	High	Direct	Consistency unknown (single study)	imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT crossover design (n=30)	High	Direct	Consistency unknown (single study)	imprecise	Undetected	<>	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Home orthostatic training vs. sham home orthostatic training								
Improved overall function	1 RCT (n=36)	High	Imprecise	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient

Appendix K. Strength of Evidence Table

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Decreased fatigue	1 RCT (n=36)	High	Imprecise	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Qigong exercise vs. no qigong exercise								
Improved overall function	1 RCT (n=52)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+¶	Insufficient
Decreased fatigue	1 RCT (n=52)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
GET vs. no treatment or flexibility/relaxation therapy or adaptive pacing								
Improved overall function	4 RCT (n=619) 3 pooled	Medium	Direct	Consistent	Precise	Undetected	SF-36 physical function WMD 10.29 (95%CI, 6.71 to 13.88)	Moderate
Decreased fatigue	4 RCT (n=619)	Medium	Direct	Consistent	Imprecise	Undetected	+††	Low
Increased proportion working full- or part-time	1 RCT (n=59)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Decreased work impairment	1 RCT (n=475)	Low	Direct	Consistency unknown (single study)	Precise	Undetected	+	Low
Global improvement	3 RCT (n=583) 3 pooled	Medium	Direct	Consistent	Precise	Undetected	Mean CGI scores RR 1.58 (95% CI, 1.25 to 1.98)	Moderate
Improved quality of life, increased days spent at work/school	No studies							Insufficient

Appendix K. Strength of Evidence Table

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
GET vs. fluoxetine vs. combination or placebo								
Improved overall function	1 RCT (n=136)	Medium	Direct	Consistency unknown (single study)	Precise	Undetected	+	Low
Decreased fatigue	1 RCT (n=136)	Medium	Direct	Consistency unknown (single study)	Precise	Undetected	+	Low
Increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Face-to-face CBT vs. telephone CBT								
Improved overall function	1 RCT (n=65)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Decreased fatigue	1 RCT (n=65)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased work impairment	1 RCT (n=65)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Global improvement	1 RCT (n=65)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
CBT + GET vs. usual care								
Improved overall function	1 RCT (n=115)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=115)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient

Appendix K. Strength of Evidence Table

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
KQ 2b. What are the harms of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?								
Galantamine vs. placebo								
Withdrawals due to harms, rates of harms, total withdrawals, serious harms, and total harms	1 RCT (n=434)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Hydrocortisone vs. placebo								
Withdrawals due to harms, serious harms, other harms	1 RCT (n=70)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	-	Insufficient
Rates of harms, total withdrawals, total harms	No studies							Insufficient
Hydrocortisone + fludrocortisone vs. placebo								
Withdrawals due to harms, serious harms, other harms, total harms	1 RCT (n=80)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Rates of harms, total withdrawals	No studies	No studies						Insufficient
Immunoglobulin G vs. placebo								
Withdrawals due to harms, serious harms, other harms, total harms	1 RCT (n=28)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>‡‡	Insufficient
Rates of harms, total withdrawals	No studies							Insufficient
Rintatolimod vs. placebo								
Withdrawals due to harms, serious harms, other harms, total harms	2 RCT (n=324)	Medium	Direct	Inconsistent	Imprecise	Undetected	Mixed§§	Insufficient
Rates of harms, total withdrawals	No studies							Insufficient
Valganciclovir vs. placebo								
Withdrawals due to harms, serious harms, other harms, total harms	1 RCT (n=30)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Rates of harms, total withdrawals	No studies							Insufficient

Appendix K. Strength of Evidence Table

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Isoprinosine vs. placebo								
Withdrawals due to harms	1 RCT (n=15)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Rates of harms, total withdrawals	No studies							Insufficient
Fluoxetine vs. placebo								
Total withdrawals	1 RCT (n=69)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Withdrawal due to harms	1 RCT (n=69)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
CBT/counseling vs. no treatment or support or relaxation or adaptive pacing								
Withdrawals due to harms	1 RCT (n=47)	Low	Indirect	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Rates of harms	1 RCT (n=257)	Low	Indirect	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Total harms	1 RCT (n=471)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Low
Serious harms	2 RCT (n=728)	Low	Direct	Inconsistent	Imprecise	Undetected	<>	Low
Acclydine vs. placebo								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination								
Withdrawals due to harms	1 RCT (n=89)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Rates of harms, total withdrawals	No studies							Insufficient

Appendix K. Strength of Evidence Table

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Pollen extract vs. placebo								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Low sugar/low yeast diet vs. healthy eating								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Distant healing vs. no treatment								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Homeopathy vs. placebo								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Melatonin vs. phototherapy								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Home orthostatic training vs. sham home orthostatic training								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Qigong exercise vs. no qigong exercise								
Total harms	1 RCT (n=52)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Withdrawals due to harms and rates of harms	No studies							Insufficient
GET vs. no treatment or flexibility/relaxation therapy or adaptive pacing								
Withdrawals due to harms	1 RCT (n=49)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient

Appendix K. Strength of Evidence Table

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Total harms	2 RCT (n=524)	Medium	Direct	Consistent	Imprecise	Undetected	<>	Low
Serious harms	1 RCT (n=475)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Low
GET vs. fluoxetine vs. combination or placebo								
Total withdrawals	1 RCT (n=136)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Rates of harms and total harms	No studies							Insufficient
Face-to-face CBT vs. telephone CBT								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
CBT + GET vs. usual care								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
KQ 2c. What are the characteristics of responders and non-responders to interventions?								
CBT vs. no treatment								
Baseline differences	1 RCT (n=27)	Medium	Indirect	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient

Key: + = positive effect; <> = no effect; - = negative effect.
*5 studies showed overall positive effect, while 2 showed mixed effects using different measures, 1 showed negative effect, and 4 showed no ffect.
†9 studies showed positive effects, while 3 showed no effect.
‡2 studies showed positive effects, 2 showed no effect, and 1 showed a positive effect vs. support but not vs. no treatment.
§Significant increase in 1 of 3 trials, 1trial reported a significant increase vs. support but not vs. no treatment.
‖ For those blinded to treatment only, not for comparison of intervention groups.
¶Intervention scored better on mental functioning subscale, but not physical functioning subscale.
**2 of 4 studies showed a benefit, for the intervention group, while 2 showed no differences.
††3 of 4 studies showed a benefit for the intervention group, while 1 showed no differences.
‡‡More headaches in intervention group, but no other differences.
§§Some harms more frequent in intervention group, insomnia more frequent in placebo group, see Appendix H4 for details.
CBT= cognitive behavioral therapy; CFS= chronic fatigue syndrome; CI= confidence interval; CGI= Clinical Global Impression of Change score; GET= graded exercise treatment; ME= myaligc encephalomyelitis; n= sample size; RCT= randomized controlled trial; RR= relative risk; WMD= weighted mean difference; vs.= versus.